EXPERIMENTAL INVESTIGATIONS INTO THE TOXICITY OF BISMUTH WITH SPECIAL REFERENCE TO ITS ACTION ON THE CIRCULATORY SYSTEM.

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EXPERIMENTAL INVESTIGATIONS INTO THE TOXICITY OF BISMUTH WITH SPECIAL REFERENCE TO ITS ACTION ON THE CIRCULATORY SYSTEM.

Introductory.

During the last four years bismuth has been assuming a rôle of gradually increasing importance in the treatment of syphilis. It is of moment, therefore, to understand more completely its action in the body, and this research has been undertaken with that end in view. An experimental study of the effects of intravenous injection of the metal has been made, special attention being paid to the action on the circulatory system.

The subject will be dealt with under the following heads:-

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(d) /

III. Study of the action of bismuth on the circulatory system (Contd.)

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I. HISTORICAL.

(a) Investigations into the toxicity of bismuth date from 1843 when Orfila[1] studied the action of a nitrate of bismuth on dogs. Thirty centigrams injected into the jugular vein of a dog gave vomiting and diarrhoea, tremors of the hind legs and a rapid and strongly beating heart. Convulsions then ensued and the animal died. Forty centigrams killed a dog in eight minutes. The results of these and other experiments led him to the conclusion that bismuth kills from an action on the nervous system, which is more marked if the poison be given intravenously.

(b) A detailed series of investigations were carried out by Steinfeld and Meyer[2] in 1886. They used a double tartrate of bismuth and sodium and after a preliminary study of the effects of sodium tartrate on frogs, proceeded to investigate in greater detail the action of the bismuth salt on frogs, fowls, mice, rats, rabbits, cats, and dogs. They determined the fatal dose on subcutaneous injection of their preparation as 14-20 mgs. in rats and mice, 25-35 mgs. in rabbits, and 10-20 mgs. per kilo in cats, the doses being calculated in terms of BI_2O_3.

In frogs they noted increased reflex irritability, convulsions, and slowing of the heart rate. Such irritative phenomena were followed by motor paralysis and death.

In mammals subcutaneous injection of 10-30 mgs. BI_2O_3 in the form of the tartrate gave rapidity of respiration, inco-ordination of movements and convulsions. The blood pressure fell and the heart became slow and irregular. Intravenous injection gave a more rapid onset of the symptoms with abrupt stopping of the heart and temporary recovery, and on autopsy marked dilation of the right heart.

In chronic poisoning they noticed loss of weight, gastro-intestinal irritation, stomatitis and nephritis. In conclusion they attributed the convulsions to irritation of the medulla and spinal cord and the succeeding paralysis to a further toxic action on the medulla.

(c) In the following year Dalche and Villejean[3] gave subcutaneous injections of a 20% neutral nitrate of bismuth suspended in glycerine to three dogs and one guinea-pig. Daily doses increasing from 0.3 to 3 grams were given until death supervened. They observed a more chronic form of poisoning with loss of weight, gastro-intestinal irritation and stomatitis.

(d) Balzer[4] in 1889 investigated the toxicity of a citrate of bismuth and ammonia given by subcutaneous injection to dogs. With fatal doses he noted anorexia, exhaustion, depression and dyspnoea. Post-mortem examination showed inflammation of the large gut and congestion of the liver and kidneys.

(e) /

(e) In 1897 Chassevant[6] who had written on the subject in 1842[5], reviewed and drew conclusions from the experimental work which had been done. In his article are cited the experiments of (a) Stephanovitch, who, using a citrate of bismuth and ammonia, found that 0.6 grams subcutaneously was fatal with the post-mortem changes of fatty degeneration in the liver, kidneys and heart; (b) Feder and Meyer in 1879, who found that with the same preparation 6-8 mgs. subcutaneously gave diarrhoea, tremors, exaggeration of sensibility and inco-ordination of movements; and (c) Luchsinger, Marti and Mory in 1883, who used bismuth ammonium citrate and bismuth sodium citrate and found that 0.2 grams subcutaneously of these preparations killed large rabbits, there being noted paralysis of the heart, a fall in blood pressure and inflammation of the gut.

After discussion, Chassevant drew the following conclusions: "On doit en conclure que les sels solubles de ce métal, poisons convulsivants du système nerveux, agissent en excitant les centres moteurs de la moelle allongée a la façon de la picrotoxine, de la cicutoxine ou des sels de baryte. Cette excitation se propage au névraxe et aboutit à une paralysée généralisée du système nerveux central. Il ne semble pas influencer directement l'appareil circulatoire."

(f) No work was done on the subject for a number of years until 1922 when Didry[7] actuated by the increasing/

increasing clinical importance of bismuth, studied the toxicity of some of its soluble salts on a large number of dogs. He stated that bismuth when given intravenously, whatever salt be injected, kills by a bulbo-medullary action. After large doses a preliminary stage of vomiting, convulsions, irregularity of the heart and deep breathing was followed by incoordination of movements, motor paralysis, relaxation of the sphincters, arrest of respiration and finally arrest of the heart. Intravenous administration of doses permitting of indefinite survival gave a similar preliminary stage of excito-motor phenomena, followed at a later date by motor paresis, irregularity of the heart, anorexia, vomiting and diarrhoea. Post-mortem examinations revealed congestion of the liver and kidneys and gastro-intestinal inflammation with haemorrhage.

(g) In the following year Pacella[8] noted that the intravenous injection of fatal doses of bismuth sodium tartrate in rabbits gave convulsions, and arrest of the heart and respiration before death. With smaller doses he noted that death was preceded by loss of weight and symptoms of gastro-intestinal irritation.

(h) In the same year Fritz[9] showed that intravenous injection in rabbits of potassium bismuth tartrate gave spasms, dyspnoea and heart failure before death.

Summary/

Summary.

No satisfactory standardisation of dosage can be made from the experiments quoted in the history, for different preparations of bismuth have been used; in some of the experiments the bismuth metal content of the preparation has not been considered and in others the weights of the animals or the dose per unit of weight have not been determined.

Many of the observers agree that large doses (doses multiples of the fatal dose) of bismuth have an irritative effect on the nervous system and that death occurs as the result of this effect. Moreover, there have been noted disturbances in the circulatory system and, in chronic poisoning, gastro-intestinal irritation. But no conclusions can be come to on the relative importance of the various effects noted or on the relation of the size of the dose to these effects. And there is no detailed account of the causes of the symptoms.

II. /

II. GENERAL TOXICITY.

(a) Lethality.

Since 1921 when bismuth made its début in the therapeutics of syphilis, a number of investigations have been made into the toxic and fatal doses of its various salts and preparations. The following are the results where intravenous injection has been used.

In 1921 Sazerac and Levaditi[10] found that 20 mgs. of bismuth ammonium citrate per kilo. killed rabbits in three days. Later in 1922[12], they used the tartrate of bismuth, sodium and potassium and found that 5 mgs. per kilo. caused death in seven days, 10 mgs. in three days, and 20 mgs. in two days, in rabbits.

Didry[7] used the tartrate of bismuth potassium and sodium on dogs and found that 10 mgs. per kilo. of the metal given as the above salt caused death in $2\frac{1}{2}$ days, and 4 mgs. caused death in $4\frac{1}{2}$ days.

Giemsa[11] in 1922 with a bismuth tartrate estimated the fatal dose in rabbits as 7 mgs. of bismuth metal ker kilo.

Jeanselme, Chevalier, Pomeret, Blamoutier and Joann[13] say that 100 mgs. per kilo. of bismuth tartrate cause instant death in rabbits.

Pomeret and Didry[14] found that 10 mgs. bismuth metal per kilo. given as tartrate of bismuth, potassium and sodium caused death in a dog in $2\frac{1}{2}$ days.

Pacella/

Pacella[8] states that 6-8 mgs. per 100 grams. in the rabbit of tartrate of bismuth and sodium (33% metal) is fatal.

Fritz[9] finds that 10 mgs. per kilo. of potassium bismuth tartrate is fatal in the rabbit, and

Muller, Blass and Kratzeisen[15] state that 1.7-5.1 mgs. per kilo. of bismuth metal of the same preparation is fatal in the rabbit.

These findings vary within considerable limits, the result, doubtless, of the multiplicity of forms in which the metal has been injected.

I have tested the lethality of bismuth in rabbits and cats.

Preparation used and Technique.

In these experiments a double salt, the tartrate of bismuth and sodium, containing 44.5% of bismuth metal, was used. The salt is in the form of whitish scales and soluble in four parts of cold water. The tests for arsenic and lead which were carried out proved negative. In all experiments the intravenous route for injection was used and the doses injected are stated in terms of their bismuth metal content. In rabbits the doses were injected into the marginal vein in the ear and in cats into the internal saphenous vein after exposure by a small incision. For injection the salt was dissolved in Ringer's solution, each dose being made up to less than 1 c.c. bulk and sterilised by heat

before being injected at body temperature. The symptoms which were noted have been discussed in a later section.

(1). Experiments on Cats.

No.of Expt.	Wt. of animal in grams	Dose of bismuth metal in mgs. per kilo.	Dose of bismuth salt in grams per kilo.	Remarks.
1	2005	17.8	0.04	Death in 18 hrs.
2	2500	13.4	0.03	Death in 13 hrs
3	2800	11.12	0.025	Death in 60 hrs
4	1600	8.9	0.02	Death in 4 days
5	2270	4.45	0.01	Death in 5 days
6	2390	2.22	0.005	Recovery: slight effects.

(2) Experiments on rabbits.

No.of Expt.	Wt. of animal in grams.	Dose of bismuth metal in mgs. per kilo.	Dose of bismuth salt in grams per kilo.	Remarks.
6	1425	2.22	0.005	Recovery; no effects
8	1725	4.45	0.01	do. do.
13	1560	8.9	0.02	do. slight effects
15	1205	13.4	0.03	do. do.
11	1005	15.62	0.036	do. do.
19	1165	17.8	0.04	do. marked effects
16	1305	22.3	0.05	do. do.
3	1425	22.3	0.05	Death in 2½ hrs.
17	1350	26.8	0.06	Death in 16 hrs.
20	1325	26.8	0.06	Death in 30 hrs.
18	780	31.2	0.07	Death in 45 mins.
7	2445	31.2	0.07	Death in 12 hrs.

Summary of Results.

The minimum fatal dose in rabbits is in the region of 22 mgs. bismuth metal per kilo. The minimum fatal dose in cats is in the region of 4.5 mgs. bismuth metal per kilo.

The/

The above experiments are quoted as typical of a larger body of results. Again, no more detail has been carried out in determining the minimum fatal dose than can serve a useful purpose.

(Contd.) (b) Maximum dose tolerated without symptoms.

The following are the results of previous investigations where intravenous administration was used:-

Fourcade, Jalloustre and Lemay[16] using a suspension of an oxide of bismuth in oil intravenously in dogs state that 100-400 mgs. are supported without symptoms.

Grenet and Drouin[17] state that 100 mgs. of a phenol derivative are borne in rabbits.

Giemsa[11] found that 0.7 mgs. metal per kilo. of bismuth tartrate is tolerated in the rabbit.

Muller, Blass and Kratzeisen[15] state that 1 mg. metal per kilo. of the tartrate of bismuth and potassium is supported without symptoms in the rabbit.

Lacapere and Galliot[18] found that 1 mg. per kilo. of colloidal bismuth in the rabbit does not provoke symptoms, and

Pomaret and Didry[14] state that 3 mgs. metal per kilo. of tartrate of bismuth, potassium and sodium is supported in the dog.

The following experiments were carried out on rabbits, using a technique similar to that discussed under/

under the preceding chapter. The results are given in the following table:-

No.of Expt.	Wt.of rabbit in grams.	Dose of bismuth metal in mgs. per kilo.	Dose of bismuth salt in grams per kilo.	Remarks.
1	1220	0.44	0.001	No effects
4	1650	1.1	0.0025	do.
6	1425	2.22	0.005	do.
8	1725	4.45	0.01	do.
10.	1310	6.67	0.015	do.
13	1560	8.9	0.02	Recovery;loss of weight
14	1450	8.9	0.02	do. do.
15	1205	13.4	0.03	do. do.
2	1250	13.4	0.03	do. do.
19	1165	17.8	0.04	do. do.

Summary of Results.

The maximum intravenous dose which is tolerated without symptoms in rabbits is 6.67 mgs. bismuth metal per kilo.

.(Contd).

(c) Observations on Poisoned Animals.

In this chapter there will be considered the effects produced by the intravenous injection of the bismuth salt in unanaesthetised animals. In a number of the experiments observations were made on the distribution of bismuth in the body, on the rate of its excretion by the urine, and on the urinary changes. Some of these observations are included in the account.

An/

An account of previous investigations into the symptoms and signs observed after injections of bismuth will be found at the beginning of the paper.

Distribution of bismuth in the body and its excretion.

In 1873 Bergeret and Mayençon[19] poisoned rabbits with a bismuth salt. After death they determined the presence of the metal in the urine, kidneys, liver, blood, spleen, muscles and intestinal tract.

In 1886 Steinfeld and Meyer[2] found that after subcutaneous injection of bismuth tartrate, the metal appeared in the urine in 10-15 hours and disappeared on the 18th day.

Dalchè and Villejean[3] state that bismuth is excreted into the urine and that its presence there turns the urine black, the result they say, of the formation of bismuth sulphide when the urine decomposes. In dogs which had received repeated subcutaneous doses of bismuth nitrate, they estimated quantitatively the amounts of bismuth in the organs. It was present to the greatest extent in the spleen and in lesser amounts in the kidneys, salivary glands and liver.

Balzer[4] in 1889 found that bismuth is excreted in the urine for 17 days after its subcutaneous injection in dogs.

Demelin[22], using the reaction advised by Leger and Aubry, estimated the rate of elimination of bismuth/

bismuth in the urine of patients. He states that it can be found 18 hours after the intramuscular injection of 0.2 grams of the citrate and disappears in 20 days. He ascribes the black colour which is observed in the urine containing bismuth which decomposes, to the formation of indoxyl-sulphide, as he found a large amount of indoxyl in the urine. He states also that bismuth was present in small quantities in the blood from his patients.

The presence of the metal in the brain has been demonstrated by Fairley and Burrell[20] and Lemay and Jalloustre[21]. They showed the presence of demonstrable quantities of bismuth in the brains of patients who had died while undergoing treatment by intramuscular injections of bismuth salts.

Fournier and Guenot[26] studied the elimination of a bismuth tartrate in patients. After 2.5 grams intramuscularly they found the metal in the urine from the 18th or 20th hour to the 20th or 30th day.

Lomholt[23] states that in man after intramuscular injections the daily excretion occurs in the urine and the faeces in the proportion of two-thirds in the urine and one-third in the faeces. The daily elimination varies between 0.5 mgs. and 4 mgs. per cent. of the amount injected.

Bardet[27] in patients found that the excretion in the urine lasted from the 20th hour to the 25th or 28th day after intramuscular injection.

Preparation used and technique.

The experiments were carried out on rabbits and cats. The preparation used and technique of the injections were similar to that previously described.

Method of estimation of bismuth in the organs.

The selected organs were cut up into small pieces, washed in water until the blood was removed, weighed separately, and treated in the following manner as advised by Barthe[24]. Destruction of the organic matter was carried out by a nitric and sulphuric acid mixture and the resulting solution treated with acetic acid and diluted. A stream of hydrogen sulphide was passed in until precipitation was complete, when the precipitate was collected by filtration. The metal in the precipitate was dissolved in weak hot nitric acid and, after dilution, ammonium carbonate was added and heating was carried out on a water-bath until the bismuth was precipitated as bismuth carbonate. This deposit was collected by filtration, dissolved in hot dilute nitric acid and prepared for electrolysis.

Electrolysis was carried out as advised by Kammerer[25]. The electrolyte was prepared by making up the bulk of the bismuth solution previously obtained to 200 c.c., adding 2 c.c. sulphuric acid and 1 gram of potassium sulphate. The electrodes consisted of two platinum gauze cylinders, 5 cm. high/

high by 10 cm. circumference, the anode surrounding the cathode and each having an electrode surface of 10 sq. cm. A current of two volts was passed through from storage cells for a period of 8-10 hours with the temperature at 45°-50° C. Then the fluid was syphoned off, and replaced with distilled water. The cathode was washed in ether, dried and weighed, this weight giving the amount of bismuth metal present in the solution.

Methods of detection of bismuth in the urine.

(1) Alkaloid reaction of Leger and Aubry (28).

About 30 c.c. of urine were acidified by nitric acid, evaporated to dryness and ashed. Dilute nitric acid was then added and the mixture heated and filtered. About ½ c.c. of the filtrate was mixed with 2 c.c. of the following reagent:

quinine sulphate - 1 gram
potassium iodide - 2 grams
distilled water - to 100c.c.

A few drops of sulphuric acid may be added to aid the solution of the quinine sulphate.

The reaction observed in the presence of bismuth was an immediate brick-red precipitate of quinine iodo-bismuthate. If iron be present a reddish yellow precipitate changing to brick red in about 1 minute's time occurs, but this fallacy was avoided by taking as positive only the immediate appearance of the characteristic brick red colour. The nitric acid used was, of course, as free as possible/

possible of iron. It is stated that this reaction is positive 1:600,000, but in my experiments I found it difficult to differentiate the reaction from that of iron in urine where the concentration of bismuth was less than 1:50,000.

In the majority of tests and in all which were doubtful, the following reaction was used in addition:

(2) Stannous chloride reaction.

To a few drops of 5/N stannous chloride solution, caustic potash was added until the white precipitate which formed dissolved. The urine was prepared as in the previous tests and to about 5 c.c. of the cold and approximately neutral bismuth solution which was obtained, the above mixture was added. If bismuth was present, a black precipitate appeared on shaking. Dilute caustic potash must be used and the solution must be cold or the stannite gives a black precipitate. Also, if too much caustic potash is added, a black precipitate of metallic tin will separate out.

Experiments on rabbits.

Expt. No. 1 - buck rabbit No. 13, wt. 1560 grams.

Time	Wt. of animal	Amt. of urine in 24 hours c.c.	Reaction to bismuth in urine	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks.
0 days		120				
0 "		110				
1st day	1560			26	12	Heart easily felt.
11.5 a.m.	8.9 mgs. bismuth metal per kilo.					intravenously
11.15				22	15	Animal listless and dull; heart felt with difficulty; there are some missed beats.
11.30				23	14	Animal apparently normal; heart easily felt and regular.
5 p.m.		95		26	14	Animal normal
2nd day	1560	85	++Black pn standing	26	13	do.
3rd day	1500	100	+ do.	24	12	Animal not taking food; otherwise normal
4th day		200	+	24	12	Animal normal
6th day		125	+			
7th day	1470	130	+			Animal normal
8th day		145	+			do.
9th day	1420	112	+			do.
10th day		200	?			do.
11th day	1300	220	+			do.
12th day		135	0			do.
13th day		112	0			do.
14th day		110	0			do.
15th day	1350	135	0			do.
16th day		94	0			do.
18th day	1370					

Experiment stopped.

Experiment 2. Buck rabbit No. 14, wt. 1450 grams.

Time	Wt. of animal in grams	Amt. of urine c.c. in 24 hours	Reaction to bismuth in urine	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks
0 days		100				
0 days		110				
1st day (12 noon)	1450			27	17	
12.5p.m.	8.9 mgs. bismuth metal per kilo. intravenously					
12.10 p.m.				29	19	Heart regular; only felt with difficulty. Animal listless.
12.15p.m.				25	19	Heart easily felt, regular; animal apparently normal
12.30p.m.				25	16	Animal normal; heart normal
2 p.m.				25	17	Normal
5 p.m.		95		24	16	Animal normal; heart normal
2nd day		130	+	25	16	Animal dull; disinclined to move; taking food.
3rd day	1400	110	+	25	18	Heart normal; animal dull; taking food
4th day		90	+ albumen present	25	17	Normal
5th day		170	+			
6th day		145	+			
7th day	1380	125	+			Animal normal
8th day		95	0			
9th day	1350	100	0			Animal normal
10th day		-	0			
11th day		-	0			
12th day	1350	-	0			Animal normal
15th day	1355					Animal normal
18th day	1350					Animal normal
24th day	1400					Animal normal

Experiment 3. Rabbit No. 11, weight 1085 grams.

Time	Wt. of animal in grams	Amt. of urine (c.c.) in 24 hours	Reaction to bismuth in urine	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks
0 days		85				
1st day 2 p.m.	1085			29	21	
2.15	15.6 mgs. bismuth metal per kilo. intravenously					
2.20				34	23	Heart regular but felt with difficulty; respirations deep; animal dull.
2.25				32	24	Heart irregular; some missed beats. Resp. deep; animal dull does not move; no weakness of limbs.
2.30				27	24	Heart easily felt; regular; resp. deep; animal listless.
2.35				27	22	Heart normal; resp. normal; Animal brighter and moves more
2.45				26	22	Animal normal; heart normal
5.0		95		26	20	Animal normal.
2nd day		5	++	26	24	Animal normal
3rd day	1025	110	+ black on standing	23	21	Animal not taking food; dull and does not move.
4th day	1000	120	+ do.			Same condition
5th day		125	+ do.	26	20	Animal taking food; normal.
6th day		135	+ do.			
7th day	990	135	+ do.			Animal normal
8th day		100	+			
9th day		115	+			
10th day	975	110	+			Animal normal
11th day		95	+			
12th day		300	?			
13th day		160	-			
14th day		110	-			
15th day	1010	95	-			Normal.

Experiment stopped.

Experiment No. 4. Buck rabbit No.19, wt. 1165 grams.

Time	Wt. of animal in grams	Heart rate per 10 secs.	Resp. rate per 10 secs.	Reaction to bismuth in urine	Remarks
1st day 11 a.m.	1165	34	26		
11.20	17.8 mgs. bismuth metal per kilo. intravenously				
11.25		30	28		Heart easily felt; missed beats at irregular intervals. Rabbit looks exhausted; does not move.
11.35		26	29		Heart irregular; missed beats. Breathing deep. Animal lies still.
11.40		19	27		Heart slow and regular and beats are forcible. Resp. deep. Animal lies still.
11.45		19	29		Heart slow and regular; same condition.
11.50		23	29		Heart irregular; missed beats. Animal quiet.
12 noon		29	30		Heart regular. Animal moves about.
1 p.m.		30	26		Heart regular. Animal apparently nor
2 p.m.		30	27		do. do.
5 p.m.		30	25		Same condition.
2nd day		32	28	++Black on standing	Animal not taking food; moves very little.
3rd day	1125	30	29	+ do.	Animal not taking food; otherwise normal.
4th day				+ slight amt. of albumen present.	Normal
5th day				+ no albumen	
6th day	1095			+	Normal
7th day				+	
8th day				+	Normal
9th day				+	
10th day				0	
11th day	1060			0	Normal
12th day				0	
14th day	1100			0	Normal
15th day				0	
16th day	1095			0	Normal

Experiment No. 5. Buck rabbit No. 16, wt. 1385 grams

Time	Wt. of animal in grams	Amt. of urine in 24 hours c.c.	Reaction to bismuth in urine	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks
1st day 11.30am	1385			32	19	
12 noon		22.3 mgs. bismuth metal per kilo intravenously				
12.5 pm.				24	23	Animal lies on its side; does not move; breathing deep; heart regular but felt with difficulty
12.10				22	21	Animal does not move; heart misses beats. Resp. deep.
12.15				25	16	Does not move; heart regular and easily felt. Resp. quieter.
12.30				27	16	Animal moving about; heart beats normal
12.45				27	22	Heart normal; animal moves but is dull.
2 p.m.				27	23	Animal moves about normally; heart normal.
5 p.m.				27	24	Animal normal.
2nd day		220	++Black on standing	29	16	Animal normal
3rd day	1360	80	+ do.			do.
4th day		300	+ do			do.
5th day		150	+ albumen and blood present			
6th day	1340	130	+			Animal normal
7th day		320	?			
8th day		170	+			
9th day	1290	125	0			Animal normal
10th day		140	0			
11th day		155	0			
12th day	1270	95	0			Animal normal
13th day		100	0			
15th day		--	0			
18th day	1235	--	0			Animal normal
22nd day	1310					Animal normal
25th day	1405					Animal normal

With regard to the excretion of bismuth in the urine, the results detailed above are borne out by a number of experiments which have not been recorded.

Experiment No. 6 Rabbit No. 17, wt. 1350 grams.

Time	Wt. of animal in grams	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks.
1st day 2.p.m.	1350	36	23	
2.15		26.7 mgs. bismuth metal per kilo. intravenously		
2.20		?	34	Animal lies on its side exhausted; cannot move limbs; heart not felt; breathing deep and rapid.
2.25		?	36	Animal has a convulsive struggle. Throws limbs about aimlessly; heart not felt. Respiration rapid and deep.
2.27		? not palpable	39	Another convulsion, accompanied by respiratory difficulty which passes off in 30 secs. Animal lies exhausted on its side after convulsion and cannot move its limbs. When limbs or head are lifted or moved, they fall back limply.
2.30		18	38	Same condition. Heart weak and regular.
2.35		20	25	Animal can move limbs but does so weakly. Cannot stand on legs. Heart misses beats and is weak. Breathing quiet.
2.40		20	19	Heart still irregular. Animal in same condition.
2.50		21	22	Heart stronger and regular. Animal can stand on its legs weakly.
3.0		16	18	Heart weak and irregular; animal same as above
4.0		16	17	Heart regular. Animal can walk but staggers and falls after a few steps. When it lies on its side its head droops.
5.0 /				

Experiment No. 6 (Contd.)

Time	Wt. of animal	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks
5 p.m.		21	20	Same condition
9 p.m.		10	14	Animal weak; easily exhausted. When it walks it does so unsteadily and falls easily. Heart regular but weak. Has not passed urine. Will not take food.
2nd day 10 a.m.	1360			Animal has died during night. Body is cold. Urine was passed in small quantity (about 5 c.c.) before death and there has been some diarrhoea.

Autopsy.

Abdomen. There is a small quantity of free fluid in the abdomen. The stomach is full and otherwise normal. The small intestine is empty and contracted. The large intestine is full of dark fluid matter. Its wall is congested. Bladder is empty. Kidneys are large and congested. They contain 0.66 mgs. bismuth metal per 100 grams of organ. Liver is dark in colour, nutmeg in appearance and on section is engorged with blood. It contains 1.66 mgs. bismuth metal per 100 grams of organ.

Heart. The right auricle is distended and dark in colour. The right ventricle is distended and dark. Left auricle and ventricle normal. The heart muscle contains 1 mg. bismuth metal per 100 grams of organ.

Lungs. Small quantity of free fluid in both pleural cavities. Lungs apparently normal.

Experiment No. 7. Female rabbit No.20, wt. 1325.

Time	Wt. of animal grams	Heart rate per 10 secs.	Resp.rate per 10 secs.	Remarks
1st day 12 noon	1325	39	28	
12.15		26.7 mgs. bismuth metal per kilo. intravenously		
12.20		43-Impulse weak: irregular.	22	Animal normal
12.25		41 do.	23	Animal listless
12.35		39-Impulse stronger: regular	24	Animal appears normal: resp. quiet
12.40		39 do.	22	Same
12.50		43-Impulse well felt	19	Same
12.55		43 do.	17	Animal dull; takes little interest in surroundings.
1.10 pm.		43 do.	17	Same
2.0		33	18	Same
2.15		33 do.	17	Animal dull; condition improved somewhat.
3.0		33 do.	17	Animal dull, but condition improved.
5.0		32	17	
9.0		34	16	
2nd day 10 a.m.		36 do.	17	Rabbit is listless; has not taken food; has passed urine.
12 noon				Condition same
2 p.m.		30-weak	19	Animal more exhausted. Its head droops and its eyes are lustreless. Lies on its side.
4 p.m.		14-irregular.	21	Animal does not move; lies as if paralysed but can move its limbs if they are stimulated.
5 p.m.		10-weak, irregular	10	Animal more helpless; cannot move now even if stimulated.
5.10		7-slow and weak	stopped	
5.12	1320	0	0	Animal dead. Has passed 30 c.c.of urine since experiment started.

Experiment No. 7 (Contd.)

AUTOPSY.

Abdomen. There is some free fluid in peritoneal cavity. Stomach distended. Its mucosa is normal. Small intestine contracted and empty. Large intestine full of dark fluid contents and its mucosa is injected.

Spleen.- Normal. Trace of bismuth metal present.

Bladder- empty.

Kidneys are slightly inflamed and contain 0.83 mgs. bismuth metal per 100 grams of organ.

Liver - nutmeg appearance. Friable and full of blood. Contains 0.9 mgs. bismuth metal per 100 grams of organ.

Heart - right auricle and right ventricle are distended with blood and dark in colour. Left ventricle and auricle normal.

Lungs - apparently normal. There is some free fluid in pleural cavity.

Experiment No. 8. Rabbit No. 18, wt. 780 grams.

Time	Wt. of animal grams	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks
11.45am.	780	28	22	
12 noon		31.2 mgs. bismuth metal per kilo. intravenously		
12.5 pm		26-impulse weak	24	Ataxia when animal tries to walk. Breathing is deep and rapid. Animal is dull and pays little attention to outside matters.
12.10		?-impulse not felt	25	Condition the same
12.15		do.	25	There is marked weakness of the muscles of the limbs and particularly the hind limbs. Animal cannot stand on its feet and there is drooping of the head.
12.25		12-impulse weak: regular.	20 breathing quiet	Above condition more marked. Animal lies on its side and does not move. Head falls limply when raised.
12.30		12-impulse weak:irregular.	16	Same
12.40		-	-	Same
12.45		-	-	Animal dead

AUTOPSY.

Abdomen. Stomach and small intestine normal. Large intestine distended and its wall is dark in colour.

Liver - dark in colour and congested.

Kidneys - apparently normal.

Bladder - contains 5 c.c. of urine which does not give a reaction to bismuth.

Heart - right side of heart distended and dark in colour. This is especially the case in the right auricle. Left heart normal.

Lungs - normal.

Summary of Experiments on Rabbits.

There is no necessity to differentiate between the symptoms following toxic but non-fatal, and fatal doses, for it was seen that the differences were merely those of intensity and rapidity of onset. In every case, and especially where large doses were given, there was noticed a preliminary stage where alterations in the rhythm and force of the heart beat were manifest. In duration this stage lasted from about three minutes after the injection until twenty minutes or half-an-hour, and improvement, though short after large doses, was observed in every case. A few other symptoms accompanied this preliminary stage, and these seem to have a secondary connection with the cardiac changes. These symptoms were: increased depth and rapidity of respiration, exhaustion and listlessness of the animal and, in one case, convulsions suggestive of cerebral anaemia. With improvement in the cardiac condition these symptoms passed off.

Where death of the animal took place a recurrence of the alterations in the rate and rhythm of the heart was a constant finding and, as before, it was accompanied by changes in respiration and attitude. Even complete inability to move the limbs was seen. It is true that such a condition may have a cause other/

other, or in addition to, that of cardiac failure, and this will be discussed in more detail in a later chapter.

The post-mortem changes of distension of the right heart, fluid in the pleural and peritoneal cavities, and congestion of the liver and kidneys, help to focus attention on the circulatory system. But that the circulatory system is not the only one affected is shown by the occurrence of anorexia, diarrhoea and loss of weight. Loss of weight particularly, is a constant sign, the other two being dependent to a greater extent on the dose.

Rate of Excretion of Bismuth by the Urine.

The recorded experiments show that, after small doses of bismuth intravenously, the metal can be detected in the urine from the first to the fifth or seventh days.

Experiments /

Experiments on Cats.

The preparation used and the technique of the injections have been described previously.

Experiment No. 1 - cat, wt. 2005 grams.

Time	Dose of bismuth salt as mgs. of metal per kilo.	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks
3.45pm.		31	10	
4.0	17.8 mgs. intravenously			
4.10				Cat is dull; pays little attention to surroundings.
4.15			15	Cat dull; head droops; moves little
4.20		12 impulse irregular	16	Cat lies in quiet condition; can be roused but pays little attention to weak stimuli. When it walks, it does so unsteadily.
4.30		16 impulse weak and irregular	18 breathing deep	The limbs are weak and cat lies on its side. Head droops.
4.45			17 do.	Condition the same
5.0		22 impulse weak; irregular	17 quieter breathing	There has been diarrhoea. Cat is weak, does not move unless stimulated and then only slightly. Lies on its side.
9.0		19 impulse stronger, regular	16 deep breathing	The animal takes more interest in its surroundings and can walk with less ataxia. Has not taken and will not take any food.
Next day 9.45 am.		12 impulse regular weak	20 deep and laboured	The breathing is laboured. Animal is exhausted and lies on its side unable to stand up. Only moves slightly when stimulated. Every 2-3 minutes there is a spasmodic movement of the trunk and limbs accompanied by difficulty in breathing which lasts 10-30 secs. and then passes off.

Experiment No. 1 (Contd).

Time	Dose of bismuth salt as mgs.of metal per kilo.	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks
10 a.m.		10 impulse regular weak	22 deep and laboured	The exhaustion is more profound. Has not passed any urine; slight diarrhoea.
10.10		8 impulse weak	17	Respiratory spasms are more frequent. There are fine tremors of the muscles of the limbs and trunk
10.15		0	0	Animal died during a spasm which was accompanied by respiratory difficulty.

AUTOPSY.

Abdomen - There is a small amount of free and clear fluid in the peritoneal cavity.

Liver - is dark in colour and full of blood.

Kidneys - congested.

Bladder - empty.

Large intestine - is empty and wall is dark in colour and congested.

Heart - The right auricle and right ventricle are dark in colour and dilated. Left side of heart normal.

Lungs - apparently normal.

Weight of animal - 2000 grams.

Experiment No. 2.

Cat, wt. 2500 grams. 0.03 grams Bismuth sodium tartrate per kilo, intravenously(13.4 mgs. bismuth metal per kilo).

Time	Dose of bismuth salt as mgs. of metal per kilo.	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks
1st day 11.45 am.		36	12	
12 noon	13.4 mgs bismuth metalper kilo intra-venously			
12.10				Animal appears normal
12.15		30 irregular	14	Cat pays less attention to surroundings; lies on its side.
12.30		31 impulse weak and irregular	14	Same
1.5 p.m.		28 weak	18	Same
2.0		? regular		Apart from some dullness and lessened reaction to touch stimuli the cat is normal.
3.0		22 regular	13	Same
4.0		-	-	Same
5.0		-	-	Same; not taking food
9.0		24 impulse regular	14	Same; has not passed urine
Next day 9.30 am.		32 regular	17 shallow	Animal has not taken any milk; is dull and inattentive and does not react to stimuli. It lies on its side, does not move and stays in any position in which it is placed. It cries when its skin is nipped.
10.0		30	19	Condition is similar. When snout is tapped with a ruler, the reflex movements of eyelids are slow.

11.0/

Experiment No. 2 (Contd.)

Time	Dose of bismuth salt as mgs. of metal per kilo.	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks
11 a.m.		29	22	Animal has a convulsion lasting 30 secs. The convulsion is of a tremulous character and passes gradually over the muscles of the body. Breathing deep during the convulsio
11.10		-	-	Another convulsion of the same duration and type. After the convulsion the animal is inattentive to touch stimuli. Face reflex is the same as before.
11.30		29 impulse regular	27	Animal lies exhausted on its side. If its head is lifted, it gradually falls back to the floor. Cries if skin is nipped but does not move
11.40		29	28	Same
11.45		31 regular	28-21	Respiration irregular in rate and depth
11.55		28 do.	20	There are fine tremors passing over all the muscles of the body
12 noon		30	11	Same
12.2		-	-	There is a convulsion of 30 sec. duration. This at first clonic and then becomes tonic in character. Twitchings of limbs and superficial muscles present after convulsion.
12.10		30 regular	20	Animal has had another convulsion similar in type. Lies on side and does not move between fits.
12.23		28 do.	33	Another and more violent convulsion There was opisthotonos during the convulsion. The convulsions now occur every 4 or 5 minutes and can be induced by tapping the animal. Face reflex more active than befor
12.35		-	-	A stimulus excites a convulsion. Face reflex active. If hands are clapped, the animal starts.
12.40 /				

Experiment No. 2 (Contd.)

Time	Dose of bismuth salt as mgs. of metal per kilo.	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks
12.40		27	31	Less irritable. No convulsions. Exhaustion extreme.
12.45		-	-	Another convulsion, same type.
12.55		26	19	Do. Animal other wise the same.
1.5 p.m.		16	14	Convulsions every few minutes and death during a convulsion. There has been no diarrhoea nor has the animal passed any urine during the day.

AUTOPSY.

Abdomen - The stomach is full but otherwise normal. Small intestine empty. Large intestine full of dark fluid matter, and its wall is congested.

Liver - is congested and dark in colour.

Kidneys - are inflamed and enlarged.

Bladder - contains about 5 c.c. of black and thick urine which gives a strong reaction to bismuth. No blood present in urine. Trace of albumen.

Heart - Right side of heart is dilated and dark in colour. Left side normal.

Spleen - normal.

Lungs - normal.

Animal's weight after death - 2460 grams.

Experiment No. 3. Cat, wt. 2800 grams, 0.025 grams bismuth sodium tartrate per kilo intravenously (11.1 mgs. bismuth metal per kilo).

Time	Dose of salt as mgs. bismuth metal per kilo.	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks
11.45am		38	16	
12 noon	11.1 mgs. bismuth metal per kilo			
12.10pm.		36	16	Normal
12.20		-	-	Cat is quiet and does not move much.
1. 0		31 irregular	17	Same
2.0		do. 28	16	Cat is disinclined to move. If disturbed it resents interference but not actively.
3.0		-	-	Same
4.0		-	-	Same
5.0		25 regular	19	Inattentive to surroundings. Quiet; has not taken any food.
9.0		24	22	Same
Next day.				
10 a.m.		26 regular	18	Quiet. Has not taken milk. If disturbed, it moves normally
12 noon		-	-	Same
3 p.m.		-	-	Same
5 p.m.		29	15	Condition the same
9 p.m.		26	14	Same
Next day.				
10 a.m.		18	19	Limbs weak, this being more marked in the hind legs which are not moved. If the animal is hurt, it cries. Pays no attention to surroundings and does not move when touched or nipped. If a noise it made, it starts. Lies on its side.
11.0		-	-	Same
12 noon		17	16	Same
2 p.m.		18 regular	22	Paresis more marked in all the limbs. Animal lies exhausted and head falls to floor if raised. Twitchings of superficial muscles.

Experiment No. 3 (Contd.).

Time	Dose of salt as mgs.bismuth metal per kilo.	Heart rate per 10secs.	Resp. rate per 10 secs.	Remarks.
2.30p.m.		17	14	Same
3.0		16 weak; regular	12	Same
4.0		21	10	Animal is much weaker. Lies on its side exhausted, but can still move its limbs When touched it cries, and jerks when a noise is made.
5.0		14 weak	8 deep	Same
5.15		17 weak irregular	7	The heart misses beats. Condition of animal same.
8.0		do. 18	10	Heart misses every 3rd beat; Animal more exhausted. Does not move now even if stimulated. Appears completely paralysed and cannot be roused. Gives the appearance of being too exhausted to move. Has vomited. Slight diarrhoea.
9.0				Condition same
Next day 9.30 am.	Animal has died during the night.			

AUTOPSY.

Abdomen - Some clear free fluid in peritoneum. Large intestine dark in colour and congested. Not full. Stomach and small intestine slightly congested.

Liver - congested and nutmeg in appearance.

Bladder - contained about 10 c.c. dark coloured urine with blood and bismuth. Trace of albumen present.

Kidneys/

Experiment No. 3 (Contd.).

AUTOPSY (Contd.)

Kidneys - enlarged and inflamed.

Heart - Right side dilated and dark in colour, the auricle more particularly. Left side of heart normal. Venous system engorged. Some free fluid in pleural cavities.

Lungs - apparently normal.

Weight of animal after death - 2650 grams.

Experiment No. 4 /

Experiment No. 4. Cat, wt. 1600 grams; 0.02 grams bismuth sodium tartrate per kilo. intravenously (8.9 mgs. bismuth metal per kilo.).

Time	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks.
4 p.m.	31	16	
4.5	8.9 mgs. bismuth metal per kilo intravenously.		
4.7	8 irregular	25	Heart beats slowly and irregularly in time and force. Breathing deep and rapid. Cat does not move and meows plaintively.
4.10	8 do.	24	Breathing deep. Heart irregular. Animal pays no attention to surroundings and seems to be wholly concerned in breathing. It then lies on its side and has a convulsive spasm lasting 20 secs. in which it moves its limbs purposelessly and has respiratory difficulty.
4.12	10 irregular, weak	18	Animal quiet. Breathing deep. Heart beat is felt only with difficulty. It has yawning followed by another convulsion of the same kind lasting 30 secs.
4.15	12 weak	22	Convulsive spasms every two minutes. Cat lies quiet and paralysed in the intervals.
4.18	28 irregular	?	Sighing respirations. Heart irregular. Convulsions still occur every three minutes, the animal having respiratory difficulty and crying when they are present. Between convulsion the body is limp and the animal lies on its side apparently paralysed.
4.20	not felt	?	Heart not felt. Respiratory convulsions. Lies exhausted in intervals and pays no heed to anything.
4.25	do.	13	Heart too weak to be felt. The animal breathes deeply and lies exhausted. No response to stimuli. No more convulsions.
4.27	20 irregular	15	Heart irregular in time and force. Missed beats. No more convulsions.
4.30	22 do.	14	No convulsions. Heart irregular but stronger.
4.35	26	7	Animal now paying some languid attention to surroundings and can move about. Breathing slower and quieter. Has passed urine.
4.40	26	8	Animal same. Heart regular.
4.50	28 regular	9	Animal is livelier. It now moves about its cage when before it lay still.
5.0 /			

Experiment No. 4 (Contd.)

Time	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks
5.0 p.m.	27 regular	12	Same
6.0	29	13	Animal is now almost normal. It moves about without any weakness of limbs and at intervals takes a sip of milk.
9.0	26	14	Same.
2nd day 10 a.m.	29	17	Apparently normal.
5.0 p.m.	25	16	Has taken a small quantity of milk. Animal is quieter and does not move much.
3rd day.	21	15	Same. Not taking food.
4th day. 11.0am.	19 impulse weak	21	Animal is quiet. There is slight weakness of the limbs. Otherwise normal. Appetite poor. No diarrhoea.
9.0 p.m.	-	-	Same.
5th day	-	-	Has died during the night.

AUTOPSY.

The post-mortem changes are complicated by the fact that the body has lain for some hours.

There is some free and clear fluid in the peritoneal and pleural cavities.

Liver - congested and nutmeg in appearance.

Kidneys - congested and dark in appearance.

Bladder - empty.

Large bowel - dark in colour and its contents are dark and fluid. Rest of gut apparently normal.

Heart - Appearances obscured by post-mortem changes, but right side appears to be full of blood.

Lungs - normal.

Spleen - normal.

Experiment No. 5. Cat, wt. 2270 grams: 0.01 grams. bismuth sodium tartrate per kilo intravenously (4.45 mgs. bismuth metal per kilo).

Time	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks.
2.20 pm.	26	9	
2.35	4.45 mgs. bismuth metal per kilo intravenously		
2.40	26	9	Animal apparently normal
2.42	26	7	do. do. Respiration deeper.
2.44	34 weak regular	12 deep	Animal restless. Breathing deep.
2.45	24 weak	10 normal	Animal is restless.
2.46	24 weak irregular	7 normal	Same
2.50	13 coupled rhythm	8 deep	Animal is normal
2.53	18 irregular	8 deep	Animal quieter than normal
2.55	20 missed beats occur	10 normal	Same
3,0	32 regular	10 do.	Animal normal
3.10	24 do.	8 do.	do.
3.15	28 do	10 do.	Animal is dull and quiet
3.20	33 do.	8 do.	Animal normal.
3.25	27 do.	10 do.	Animal normal.
3.40	32 do.	8 do.	do.
5.10	35 do.	9 do.	do.
Next day	32 do.	10 do.	do.
3rd day	31 do.	7 do.	Animal appears dull and listless.
4th day	normal	normal	Animal dull and resents interference. Has not taken food during last 2 days. Some diarrhoea.
5th day	-	-	Has died during the night.

Experiment No. 5 (Contd.).

AUTOPSY.

There is some free fluid in the peritoneal cavity.

Liver - congested and nutmeg in appearance.

Kidneys - swollen and inflamed.

Bladder - contains about 10 c.c. clear urine which contains bismuth and some albumen.

Intestine - both large and small is empty. Wall of large intestine is inflamed.

Heart - right auricle and ventricle distended. Left side normal.

Lungs - normal.

Weight of animal after death - 2200 grams.

Experiment No. 6. Cat, wt. 2390 grams: 0.005 grams bismuth sodium tartrate per kilo intravenously (2.2 mgs. bismuth metal per kilo.

Time	Heart rate per 10 secs.	Resp. rate per 10 secs.	Remarks
3.0 p.m.	35	10	
3.5	2.22 mgs. bismuth metal per kilo. intravenously		
3.10	22 weak regular	12 normal	Animal normal
3.15	29 irregular missed beats	10 do.	do.
3.20	30 regular, impulse weak	13 do.	do.
3.25	25 regular	12 do.	do.
3.40	24 do.	10 do.	do.
4.10	32 do.	9 do.	do.
5.10	29 do.	12 do.	do.
2nd day	32 do.	10 do.	do.
3rd day	normal	normal	do.
4th day	do.	do.	do.
5th day	do.	do.	do.
6th day	do.	do.	do.
7th day	do.	do.	do.
18th day	do.	do.	do.

Weight 2305 grams. Experiment ended.

Summary of experiments on cats.

These experiments differ from those done on rabbits in the more varied symptomatology presented, but a survey will convince that a thread of similarity runs through both.

The outstanding difference is one of dosage. Whereas in rabbits the fatal dose is 22.3 mgs. per kilo, in cats it is 4.45 mgs. per kilo, or a fifth of the fatal dose for rabbits. I have not been able to find an explanation of this phenomenon, nor does reference to the literature help, for there are no records of similar investigations.

As with the rabbits, so with cats, a preliminary stage of irregularities in the heart rate and rhythm were noticed. The stage was similar in duration and the accompanying alterations in respiration and motor power were observed. In this connection, Experiment No. 4 is of note, for there the alterations in the heart rate and rhythm and in the breathing, the onset of extreme exhaustion and the occurrence of convulsions suggestive of cerebral anaemia could leave little doubt in the mind of an observer that the fons et origo of the symptoms was circulatory failure. And here again temporary complete recovery took place.

But the symptoms which occur later and precede death in this series of experiments cannot be dismissed so easily. Here two sets of symptoms may be distinguished /

distinguished; those where there were increased reflex irritability and convulsions due to nerve centre irritation, and those where exhaustion of the animal and alterations of the heart rate and rhythm were present. These two sets seem to have a direct relationship to the dose, for the symptoms of irritation of the nerve centres occurred in two of the experiments where the doses were large and the second set of symptoms where smaller doses were given.

To review the first set - In experiment No. 2, for the few hours which preceded death on the second day, the animal suffered from increased reflex irritability and convulsions of clonic and later of tonic character, evidently due to a nerve centre irritation. In Experiment No. 3, on the third day, there was a slight increase in reflex irritability but this passed off on the next day.

In the second set, which included all experiments with the exception of No. 2, death was preceded by slowing and irregularity of the heart and the accompanying symptom complex of alterations in respiration with increasing listlessness and paresis.

The assumption that the paresis and listlessness noted in these experiments are the result of cardiac impairment is intelligible, but not justifiable unless comparison is made with the complete exhaustion noted soon after the injections in a few of the animals, and unless the findings on the action of bismuth on the circulatory system, which are recorded

in/

in a later chapter, are applied to explain these symptoms. Mention must be made of the post-mortem appearance of dilatation of the right heart, free peritoneal and pleural fluid and congestion of the liver and other abdominal organs, a combination of appearances which might well result from cardiac failure. That no other hypothesis is adequate in returning an ordered account of the experiences is more fully discussed in a later chapter.

It is true that in a number of experiments there were congestion of the kidneys and partial suppression of urine,and such a morbid pathology would reflect itself as a factor in the production of exhaustion and dyspnoea. This must constitute an additional factor of indeterminate extent in the hypothesis, but it only applies in those experiments where death takes place after a period of days.

Anorexia, diarrhoea and loss of weight occurred to a certain extent and require mention. These symptoms, when considered with the inflammation of the gut which was found post-mortem, point to a gastro-intestinal irritation which occurs in addition to the above mentioned impairment of the other organs.

The above findings are not at variance with the literature on the subject, though one is impressed by the slight amount of importance which has been attached to the cardiac impairment in acute poisoning. This cardiac impairment was noted particularly by

Steinfeld/

Steinfeld and Meyer[2], Luchsinger, Marti and Mory[6], Didry[7], Pacella[8], and Fritz[9]. They noted also, the symptoms of nervous system irritation which were more evident than those from the circulatory system. But large doses were given in those experiments where the nervous system was affected, whereas smaller doses gave an effect on the circulatory system alone. This agrees with my results in which small doses intravenously produce temporary cardiac impairment and larger doses give a more marked effect on the heart with additional symptoms of irritation of the nervous system. But I was impressed throughout the experiments by the relative importance of the action on the circulatory system.

The anorexia, nausea, vomiting, and diarrhoea and loss of weight which were noticed in my experiments in the more chronic forms of poisoning were also observed during most of the investigations in the literature.

III. /

III. STUDY OF THE ACTION OF BISMUTH ON THE CIRCULATORY SYSTEM.

There is no detailed account of this action in the literature, and such observations as have been recorded there are mentioned at the beginning of the paper.

In the experiments which I carried out on the effects of intravenous injection of bismuth on unanaesthetised animals, symptoms and signs of cardiac impairment were noted constantly. Indeed, these symptoms occasionally drowned all others by their intensity and rapidity of onset.

In the following experiments I have endeavoured to show and explain the various changes which are brought about in the circulatory system by the injection of bismuth. The subject will be treated under the following heads:-

(a) Action on the heart in situ.

(b) Action on the Blood Pressure with a comparative study of the relation between dose and effect on the circulatory system.

(c) Action on the perfused heart.

(d) Comparison with the effects produced by some other metals.

(a)

(a) Action on the heart in situ.

This was investigated in two ways. In the first the movements of the auricle and ventricle were registered graphically on a kymograph by means of levers. In the second the movements of the heart were recorded by means of electrocardiograms.

1. Graphic registration of the heart beat by means of levers.

.Preparation used and technique -

The preparation used was the bismuth sodium tartrate aforementioned, given intravenously dissolved in Ringer's solution. The experiments were carried out on dogs and cats. Paraldehyde 1 c.c. per kilo by the stomach followed by ether was the anaesthetic used in cats and morphine 20 mgs. per kilo subcutaneously followed by chloretone 0.2 c.c. per kilo intravenously and ether were used in dogs.

The dissection in dogs and cats was carried out as follows: A cannula was inserted into one of the jugular veins for the injection of solutions and another cannula into one of the common carotid arteries for blood pressure records. Under artificial respiration through a tracheal cannula, the chest was opened in the mid-line and the edges of the incised pericardium sewed to the chest wall. In cats the recording levers were connected with a hook in the apex of the heart and a clip on one of the auricles. It does not matter which auricle is used, but the

right/

right auricle was usually taken because of its greater accessibility. In dogs the levers were connected with a Cushny myocardiograph. The time taken over the preparation of the animals, was, within reasonable limits, similar in all experiments.

In some earlier work which is recorded in a later section it was found that the rate of administration of the dose played a part in the effect produced. Therefore, all injections have been spread over approximately the same length of time, namely, 8-12 seconds.

2. Graphic Registration of the heart beat by means of electrocardiograms.

These experiments were carried out on dogs and cats - mainly on dogs, however, because in them the heart rate is slower and the deflection curves are greater. The same anaesthetics were used for the animals as in the kymograph experiments, but the only dissection carried out was the insertion of a cannula into one of the veins in a leg for the injection of the bismuth solution. For electrodes, non-polarisable needles were plunged into the muscles of the limbs, their position being changed slightly by taking them out and reinserting them before each record was taken. The three leads used were: Lead 1, electrodes in left upper limb and right upper limb: Lead 2, electrodes in right upper limb and left lower limb, and Lead 3, electrodes in left upper limb and left lower limb.

The/

The movements of the string were standardised so that one centimetre of excursion represented one millivolt. The rate of the time-marker has been given with each tracing.

The details of the experiments where the heart rate was recorded by means of levers have been inserted at the end of the paper as Tables I-X. Some side notes, which were made at the time of the experiments, and later, when the records were studied, have been added. The findings in these experiments have been described in the next chapter which, in turn, is followed by an account of the electrocardiographic experiments.

Descriptive and Comparative Study of Experiments /

Descriptive and Comparative Study of Experiments.

An attempt will be made here to group and to compare the various changes which were observed in the foregoing experiments. Electrocardiograms have been inserted at the end of the section to bear out the findings obtained in the kymographic experiments.

The changes and irregularities observed in the heart were of an extremely varied nature, especially the preliminary irregularities which occurred. In all the experiments there could be distinguished a primary phase of extreme irregularity in the ventricle and a later phase where the irregularities had become steady in type. This later phase was most characteristic of the irregularities after bismuth, and will be described first.

The chief changes were auriculo-ventricular heart block of different types and marked lowering of the blood pressure. In the kymographic experiments, where artificial respiration was regularly carried out, these changes could be studied in detail. In the electrocardiographic experiments, on the other hand, artificial respiration was not carried out, so that although heart block was found, it was thought that the asphyxia which followed the cardiac impairment and low blood pressure lessened the value of the results, asphyxia itself being a potent agent in producing heart block. Consequently, few electrocardiograms of these pronounced irregularities have been/

been recorded. Moreover, the pronounced irregularities are so definite in the kymographic experiments that their confirmation by electrocardiograms is not required.

The Characteristic Irregularities in Rhythm after Bismuth.

After a transient stage of marked and unstable irregularities, the heart rhythm settled down to regular types of heart block. The rhythm of the auricle remained regular throughout, the missed beats occurring only in the ventricle.

Alterations in the rate, and systole, diastole and amplitude of the heart during these irregularities.

Marked slowing of the heart rate was constantly observed. The extent of the slowing varied with the dose of bismuth given, a decrease of 40% of the normal being noted in the auricle when auriculo-ventricular block was marked.

The systolic movement of the ventricular lever was diminished greatly in every experiment, and this was combined with an increase in diastole. But the lessening of systole was of such extent that the ventricular amplitude was much lessened. The auricle showed a diminution of its systolic movement.

Duration of auriculo-ventricular conduction.

A lengthening of the time between the contraction of the auricle and ventricle was a constant accompaniment of the irregularities. In many cases this interval was double that in the normal heart.

Duration/

Duration of the ventricular beat.

A marked increase in the duration of the ventricular contraction accompanied the lengthening of A-V conduction and the irregularities in rhythm.

Types of irregularity of the heart beat.

It has been stated above that heart block of various types are the most characteristic changes in rhythm. The types most commonly noted were 2-1, 3-1, 4-1, and 5-1 auriculo-ventricular block. More complicated types were rare. The above-mentioned changes in rate, amplitude, A-V conduction and duration of the ventricular beats were present in all the types.

Below, there are given a few records of some interesting types of heart block obtained during the experiments.

Figure 1 /

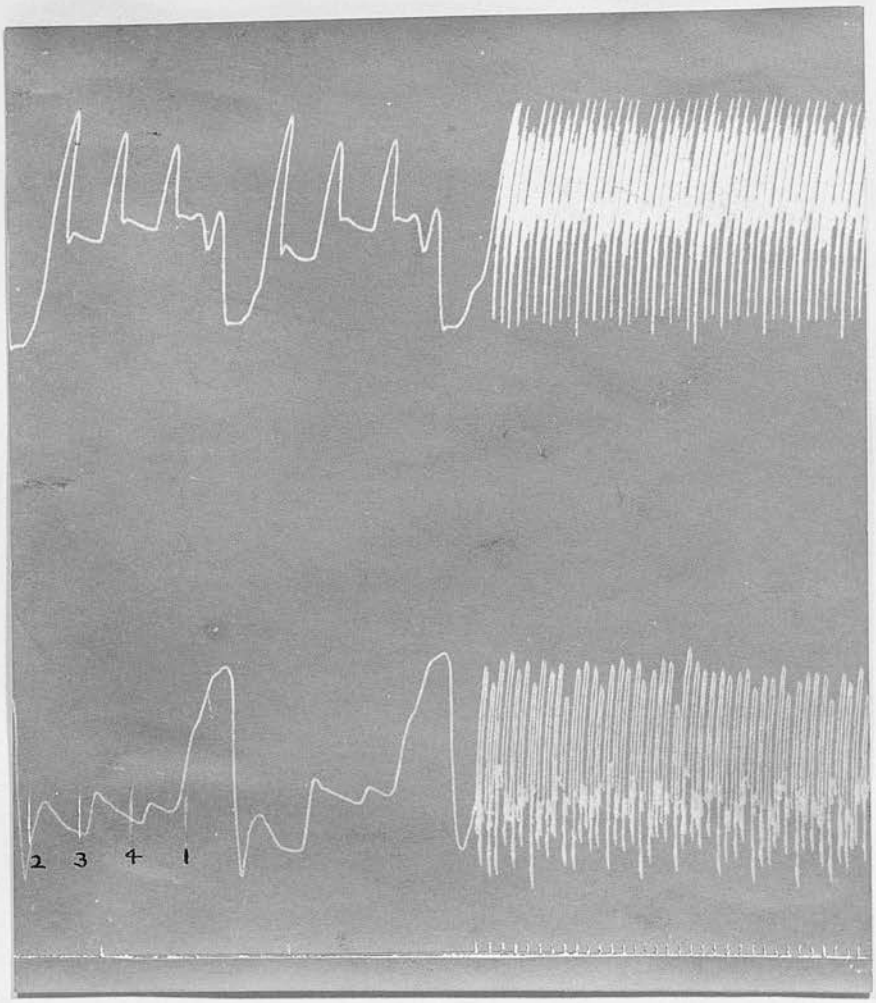


Figure 1. (from Experiment No. 6).

Auricle (upper) and ventricle (lower) from a cat in an advanced stage of bismuth poisoning. The tracing, as do all the others, reads from left to right. The upstroke represents systole, downstroke diastole. There is a 4-1 block present with a marked lengthening of the A-V intervals. The numbers 1, 2, 3, and 4 represent the incidence of the auricular beats on the ventricular tracing. (Time in 2 sec. intervals).

A /

A more common type of heart block, of which the following is an example, is that where 2-1 rhythm is present.

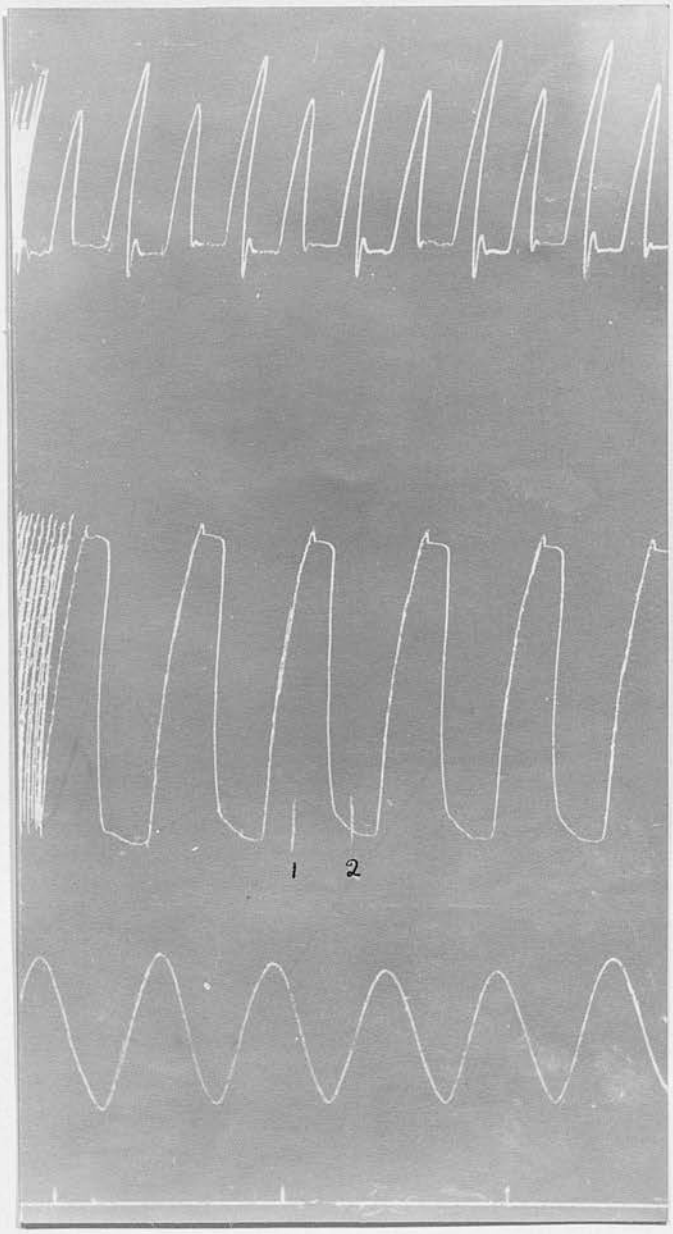


Figure 2.

Tracing from a dog's heart (Experiment No.10) after 3.12 mgs. bismuth metal have been given. Auricle (upper), ventricle (lower). The blood pressure is recorded below the heart. There is 2-1 block present with marked increase in the A-V interval. The numbers 1 and 2 represent the incidence of the auricular beats on the ventricular tracing.

The/

The alternation in the amplitudes of the auricular beats in this tracing is due to the following cause: Two auricular beats occur before one ventricular beat; there is a greater resistance to the passage of blood from the auricle to the ventricle in the second of these beats and therefore systole is less complete. The blood pressure in the tracing is low and the difference between systolic and diastolic pressures marked. (Time in 2 second intervals).

Figure 3 /

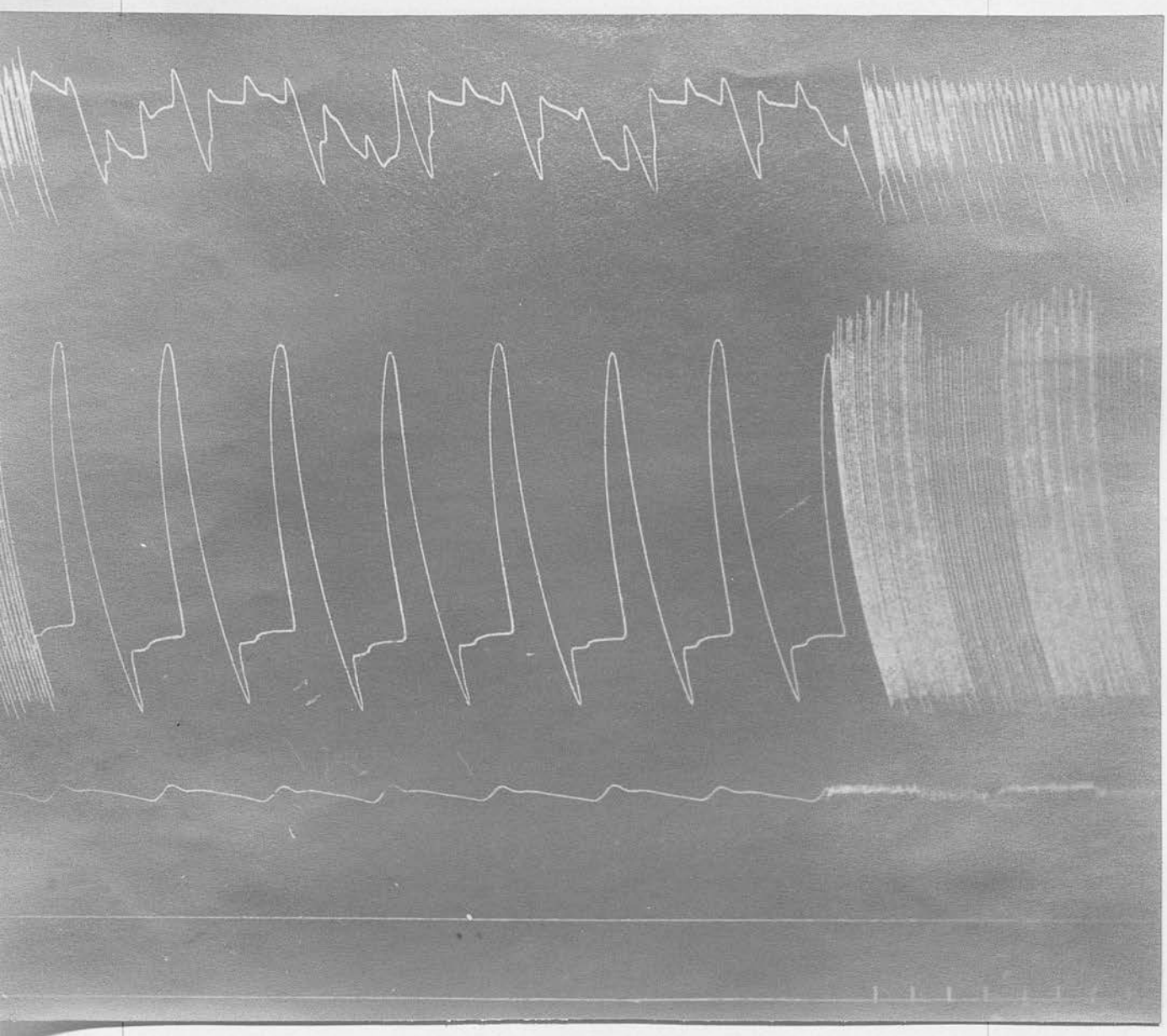


Figure 3. This tracing is from a cat's heart after 3.56 mgs. bismuth metal per kilo. The auricle is upper and the ventricle lower. Blood pressure is recorded below the heart. In the left part of the tracing there is 3-1 A-V block which changes as the drum slows to 2-1 block. There follow periods of alternating 3-1 and 2-1 heart block. Some of the auricular movement is mechanical. The blood pressure is low. (Time in 10 second intervals).

A more uncommon type of heart block was that where the ventricle only responded twice to three beats of the auricle. The following tracing is illustrative.

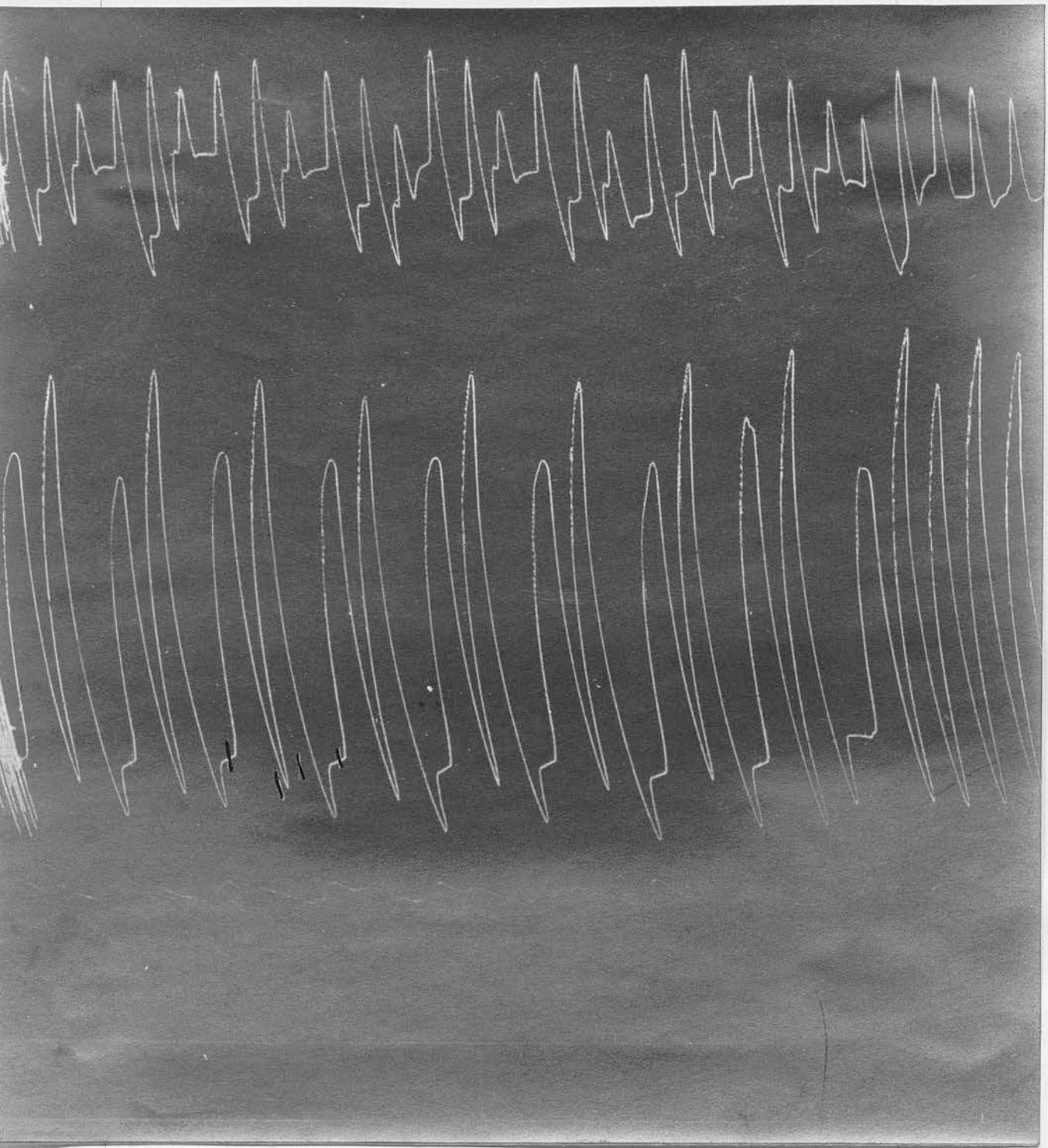


Figure 4. (From Experiment No. 3).

Tracings from the auricle (upper), ventricle (lower) /

(lower), and a blood pressure tracing from a cat in the recovery stage after 1.78 mgs. bismuth metal per kilo had been given intravenously. There is 3-2 auriculo-ventricular block with an increase in the duration of the A-V intervals and some increase in the duration of the ventricular beats. There results a coupled rhythm in the ventricle, every second beat having a more complete systole than the one which precedes it. This is because the second beat is preceded by a shorter period of diastasis; it has thus less time to get filled with blood and therefore can contract more completely than its predecessor which has to propel a larger quantity of blood. (Time in 10 second intervals).

The changes described above were preceded invariably by a short and transient stage where a number of interesting irregularities were present. The duration of this stage was regulated by the dose of bismuth given, or the rate of its injection, but usually it lasted for a short time only. These irregularities will not be considered in much detail for they represent what is evidently only a transition stage. A few tracings are shown to illustrate the various types of irregularity and the changes in the rate, amplitude and conduction of the heart are discussed with the tracings.

Figure 5 /

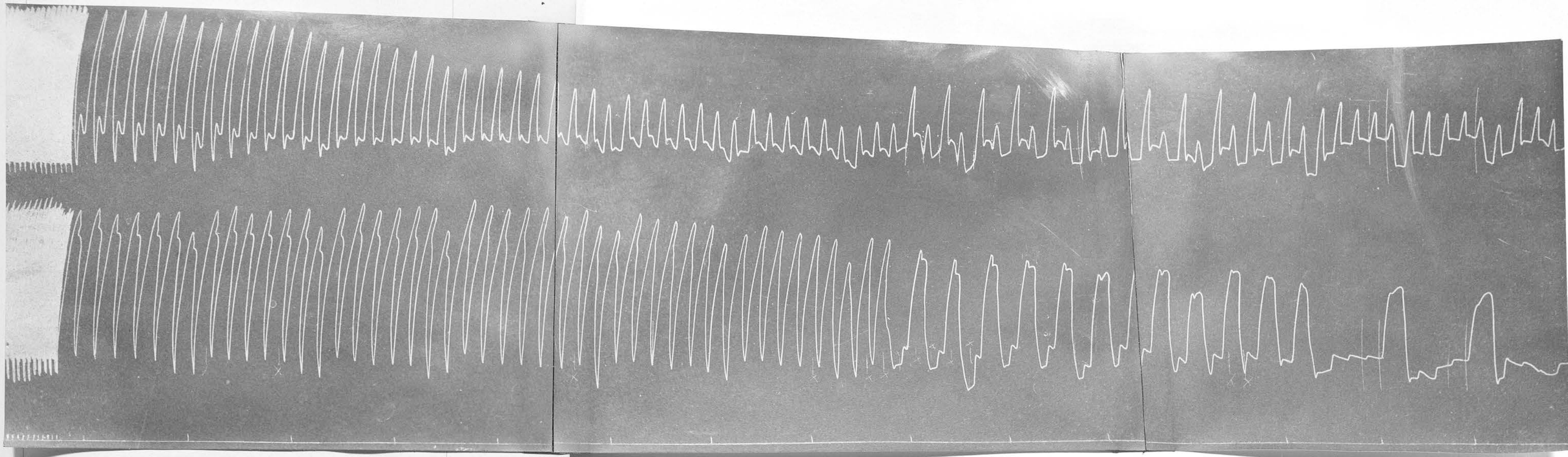


Figure 5. (From Experiment No. 6).

Auricle (upper) and ventricle (lower) from a cat after 3.6 mgs. of bismuth metal intravenously. There is seen the onset of heart block in a simple manner, the ventricle merely failing to respond to every second auricular impulse at first, and later only responding to every fourth auricular beat. (Time in 2 second intervals)

The above tracing demonstrates well the changes in the rate and systole, diastole and amplitude of the heart when irregularities come on. These changes are:

1. Slowing of the rate of the auricle, the decrease usually being about 15% of the normal.
2. Progressive lessening of amplitude of the auricle, systole being the movement which is the more curtailed.
3. Progressive diminution of the size of the ventricular beats, until, when the irregularity/

Figure 6.

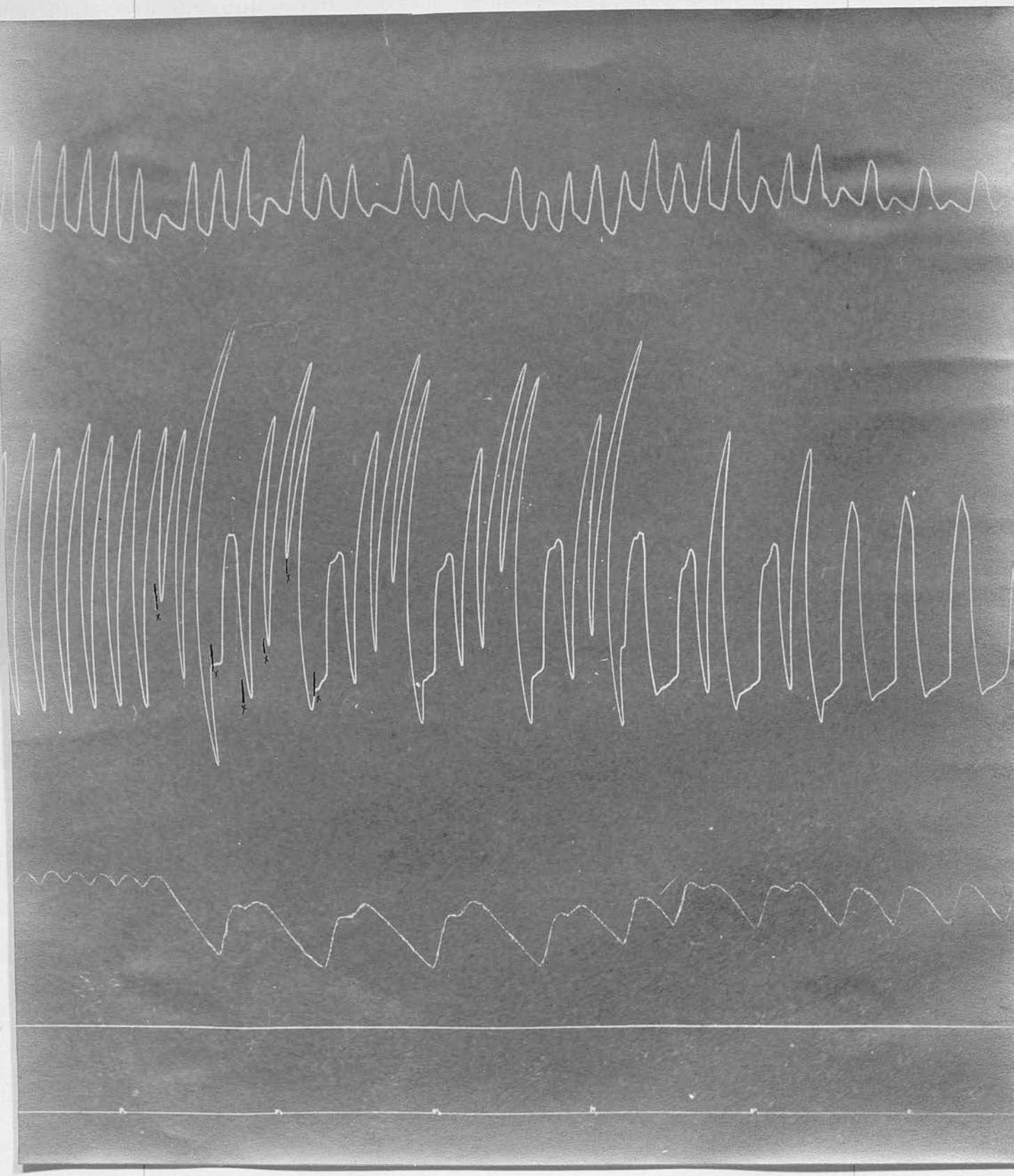


Figure 6/

Figure 6. (From Experiment No. 10).

Myocardiograph from the auricle (upper), ventricle (lower) of a dog after 3.1 mgs. bismuth metal per kilo. intravenously in two doses. There is a blood pressure record in the lower part of the tracing. (Time in 2 second intervals)

There is seen the onset of 2-1 heart block after an interval when the ventricle beats in a quadruple rhythm. In these sets of four, the first two ventricular beats follow auricular beats and the second two ventricular beats are apparently ventricular extrasystoles. The extrasystoles stop, the ventricle beats at 3-2 block and then at 2-1 block. Though on superficial examination it is not easily apparent, the auricular beats are evenly spaced throughout.

In the above tracing alternation in the size of the auricular beats is evident. An explanation of this phenomenon has been given under some of the preceding tracings.

The onset of heart block may be accompanied by yet another type of irregularity, a type which presents some features of interest. It occurred in Experiments 3, 7, 8 and 11. A variation occurs in the duration of the ventricular beat, any disturbances in the auricle being the result of changes in its blood content or of varying resistance to the blood flow from the chamber as the result of the ventricular irregularity.

The contraction of the ventricular muscle as noted by direct observation and by study of the tracings takes place in a more leisurely manner: that is, there is an increased duration of ventricular contraction. The force of the beat is not increased but the passage of the wave of contraction is slower. This being so, the next stimulus from the auricle falls on ventricular muscle which has only just relaxed or is relaxing and consequently gives rise to a small or abortive beat. These abortive beats are of shorter duration and, in fact, may only notch the ventricular downstroke. The above complex runs its course in sets of two usually , or three or even 20 beats. When heart block ensues, it does so by the gradual missing out of the small or abortive beats. A few scattered ventricular extrasystoles occasionally complicated the irregularity. Such an onset is shown in the following tracing.

Figure 7 /

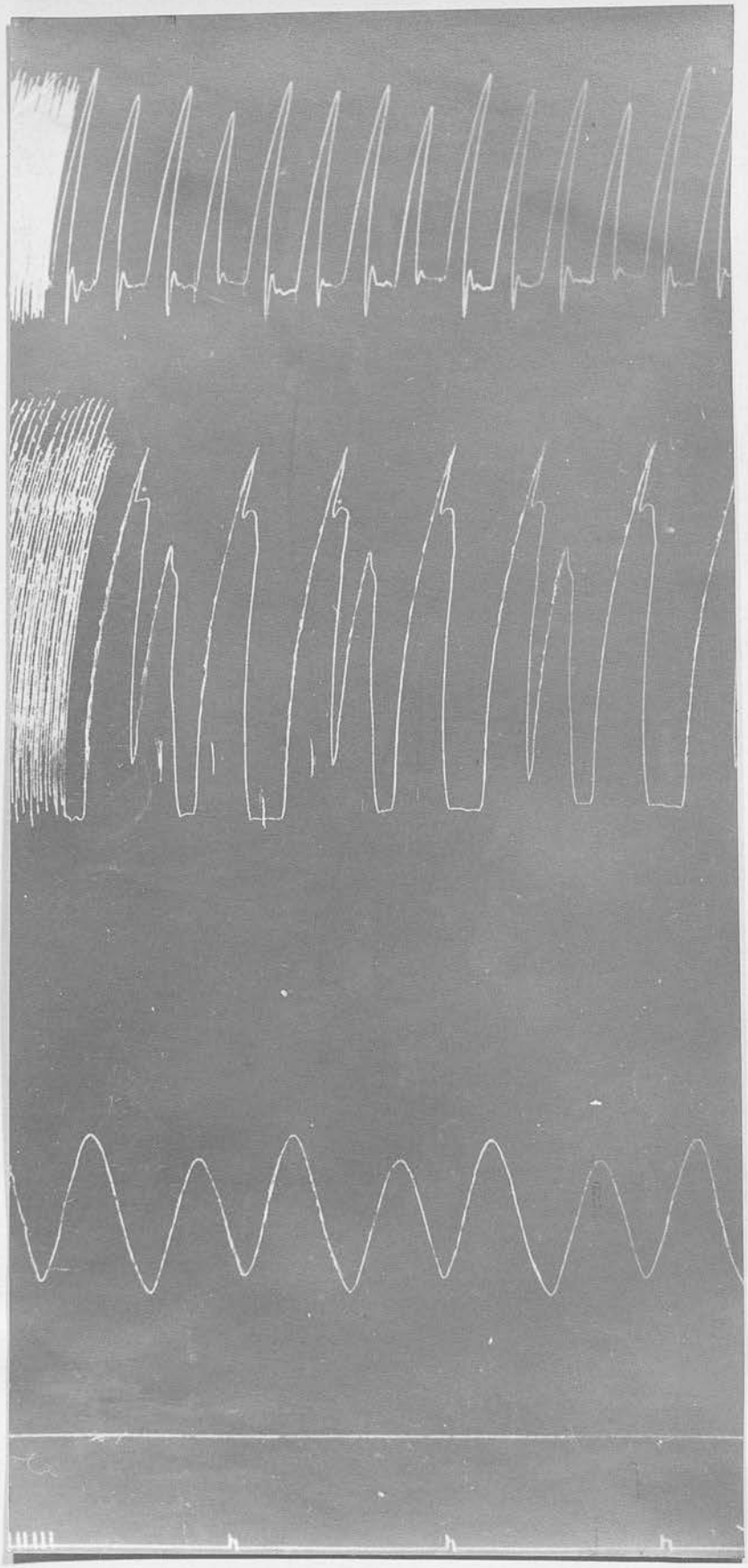


Figure 7.

Myocardiograms from the auricle (upper), ventricle/

ventricle (lower), and a blood pressure tracing from a dog (Experiment No. 7) after 1.6 mgs. bismuth metal per kilo. have been run into a vein. There is apparent 2-1 auriculo-ventricular block, but every second ventricular beat is followed by a smaller beat which follows an A-V interval of the same abnormally long duration, so that there is in reality not 2-1 block but only one ventricular beat missed in three. The abortive ventricular contractions are abortive because the auricular impulses which precede them fall on an incompletely relaxed ventricle. Thus the increase in duration of the ventricular beats is responsible for part of the abnormality. The abortive beats are not reflected in the blood pressure tracing. (Time in 2 second intervals)

The irregularities in the heart beat described above were usually preceded by a short stage where a slight fall in blood pressure, slight lessening of the amplitudes of the auricle and ventricle and slight slowing of the heart rate, occurred. Doses of 0.5 mgs. of bismuth metal per kilo. were enough to produce these changes and, indeed, such small doses gave these changes without any following irregularity.

Rate of the heart after small doses of bismuth.

With the exception of one experiment, slowing of the heart rate was a constant feature. In extent it varied with the dose, the mean change after doses between 0.5 and 1 mg. metal per kilo. being by three beats per ten seconds. The extent of the slowing may be studied more fully by reference to the records of the experiments. In the exception (Experiment No.8) slight quickening of the rate was observed.

Systole, diastole and amplitude of the heart beat after small doses.

These changes usually became manifest about 2-4 seconds after the administration of the dose. In no case did they become marked in a heart which remained regular.

These changes were: A constant and slight lessening of diastolic relaxation in both auricle and ventricle, the alteration in the auricle preceding in onset that of the ventricle. A less constant decrease is systole of the ventricle and auricle followed in three experiments by a transitory increase. As the result of these changes, the amplitudes of the ventricle and auricle were decreased at first, but in the three experiments above-mentioned a transitory increase in the ventricular amplitude occurred. These changes are illustrated in the following tracing.

Figure 8 /

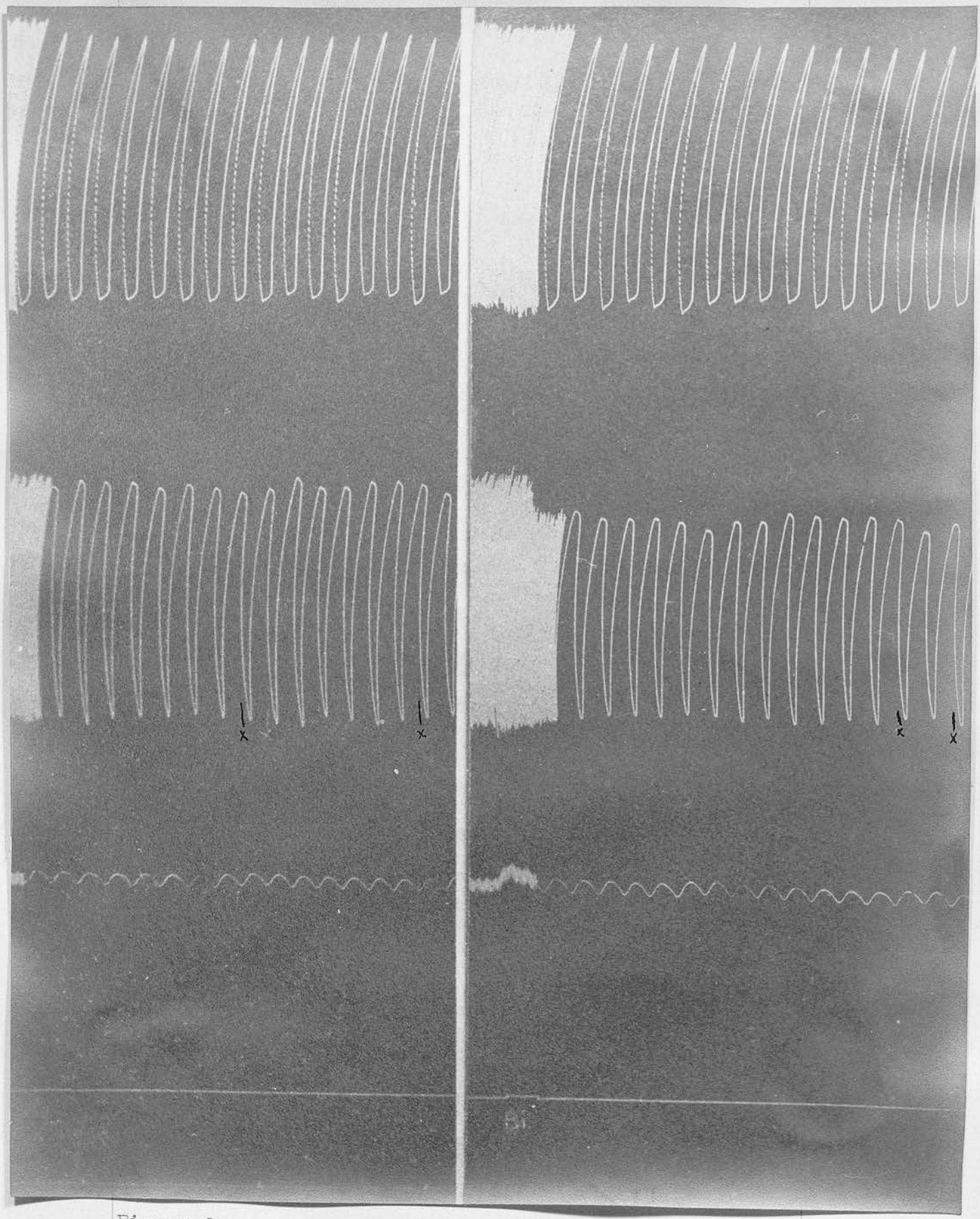


Figure 8.

Auricle (upper) and ventricle (lower) from a cat before and after a dose of 0.45 mgs. bismuth metal/

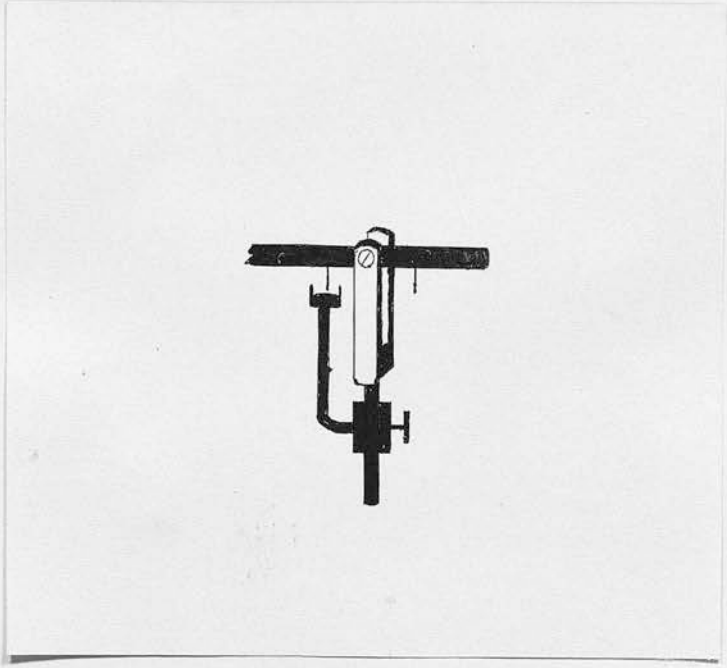
metal per kilo. The blood pressure is recorded below the heart. After the injection, the amplitude of the auricle is lessened slightly and the amplitude of the ventricle to a more marked extent. The systolic or upward movement of the ventricular lever is affected more than the diastolic or downward movement. The A-V interval is not observably altered. The blood pressure falls slightly. (Time in 2 second intervals).

A slight fall in the blood pressure was an invariable accompaniment of the first stage of alterations in amplitude. A low blood pressure might well produce changes in the auricular amplitude, and therefore the relation between the two has been discussed, but in a later section.

Excitability of the heart muscle after small doses of bismuth.

In using the word excitability here I mean the excitability of the heart muscle to electrical stimuli and not in its true sense of ability of heart muscle to respond to natural stimuli. This has been investigated in experiments on cats where the heart was exposed and tracings taken from the auricle and ventricle as in the other experiments.

An apparatus was used (Figure 9)



whereby/

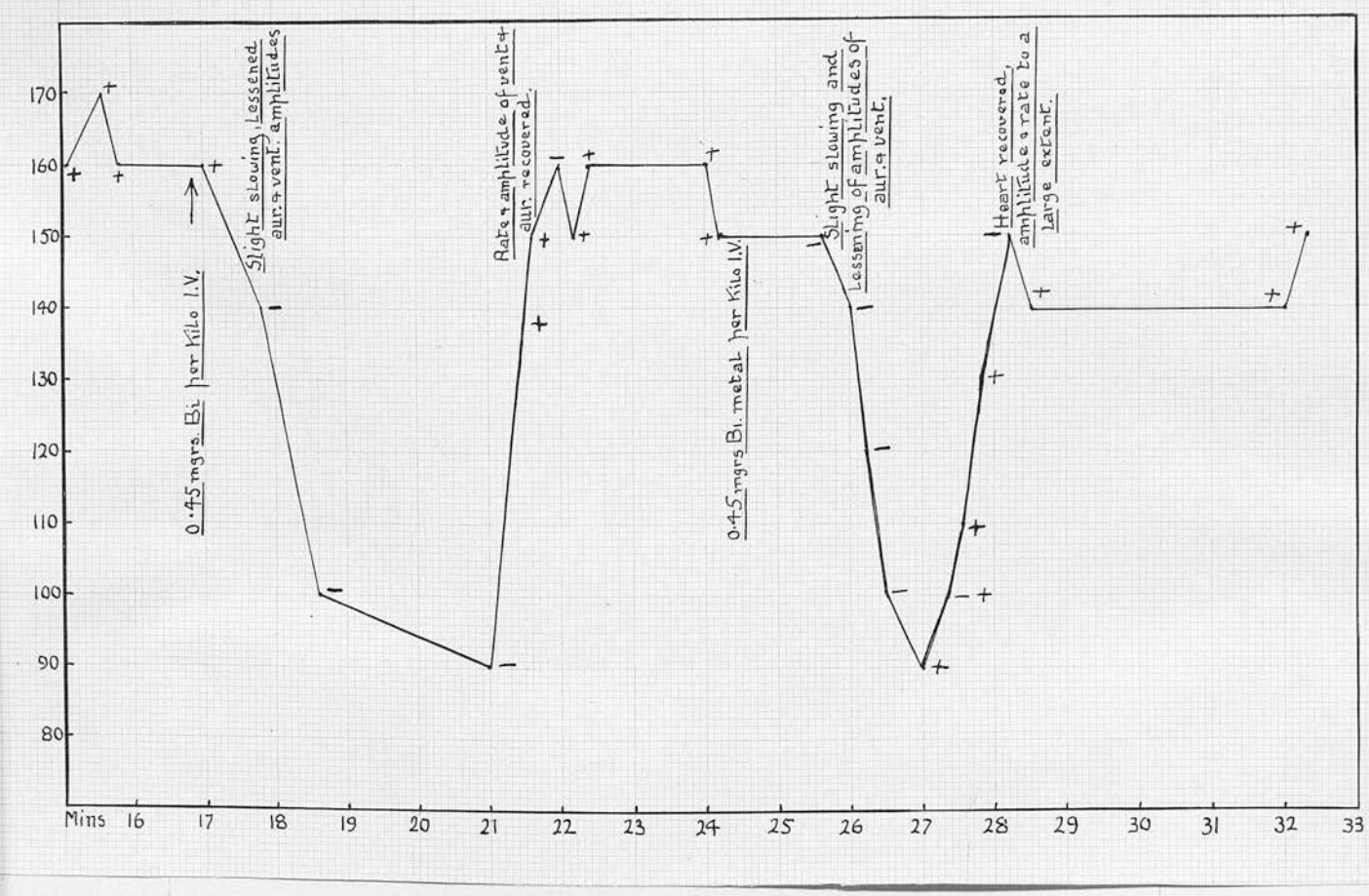
whereby a stimulus was originated when desired by the movement of the ventricular lever. I am indebted to Mr N.E. Condon for designing and making this apparatus.

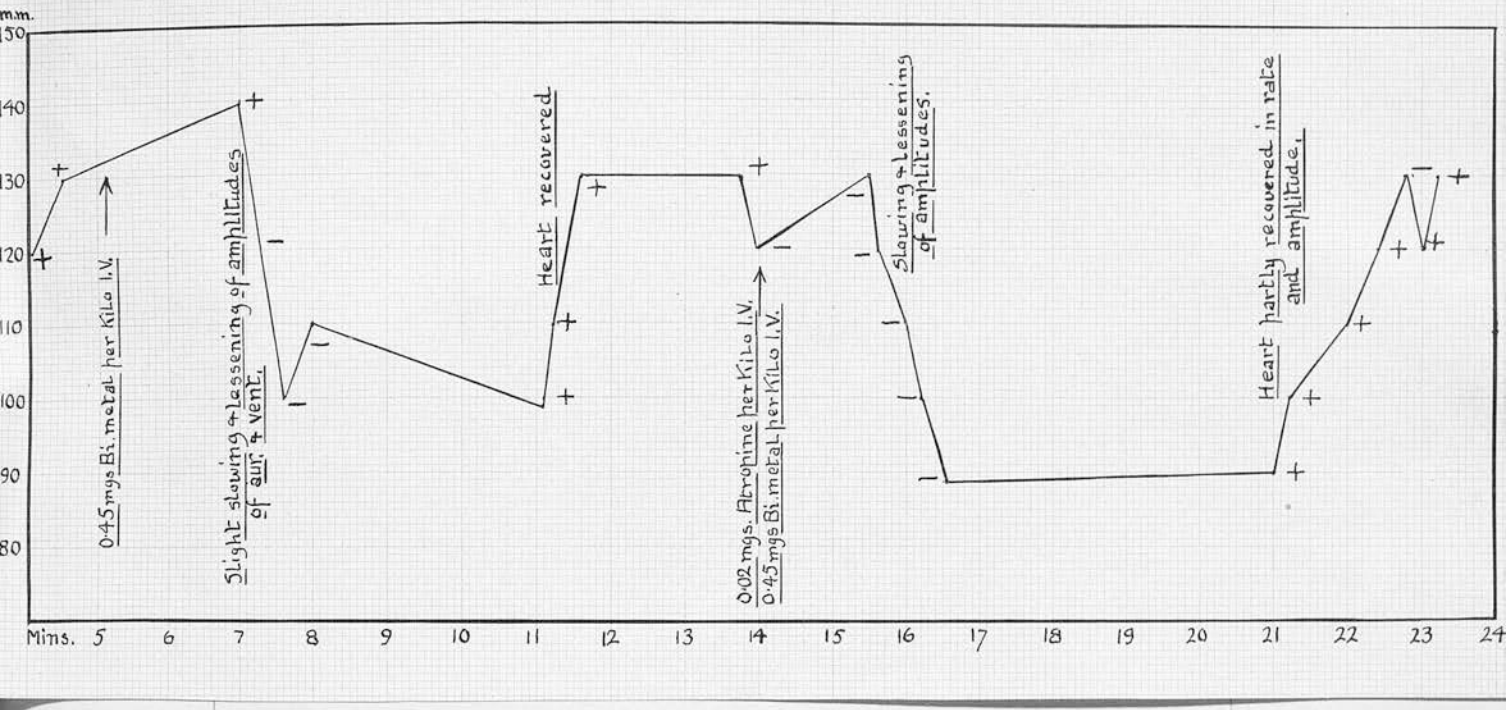
Two wire electrodes placed in the muscle of the ventricle led to coils so connected that only the break of the current gave rise to a stimulus. A mercury and wire contact was arranged on the ventricular lever so that a break of the current was made when the lever reached any pre-arranged point in its ascent or descent. This stimulus could be originated at any position of the lever merely by moving the contacts, but the only position used in the experiments was such that a break of the current was made when the lever reached a point in its descent corresponding to the last third of diastole. Each descent of the lever thus caused an electric shock to pass through the ventricle, resulting in an extrasystole and the repetition of these was shown by an acceleration of the rhythm in the heart before bismuth was injected. When the excitability of the ventricle to electric shocks is lowered, the refractory period is deepened or prolonged and then the shocks cause no extrasystoles or a less constant series of them.

Obviously this method cannot be used in a heart which shows changes in amplitude, because then the shock would occur at a different time in the movement of the lever. So that in the experiments recorded/

recorded, the doses given were of such a size as to result in no, or only slight, changes in amplitude. The results were controlled by a repetition of the procedure when the heart had recovered from the first injection.

The results of two experiments are portrayed in Figures 10 and 11, and a glance shows that there is a definite decrease in the excitability of the ventricular muscle to electric shocks after small doses of bismuth.





Figures 10 and 11.

Determination of decrease of excitability of the heart muscle in the cat to electrical shocks after bismuth.

Horizontal - time in minutes.

Vertical - distance in mm. between the coils of the circuit.

The responses of the muscle to the shocks are indicated by the + or - signs on the tracings. Two injections of bismuth have been given in each experiment, the second dose in the second experiment being preceded by an injection of atropine.

This decreased excitability reached its height in 2½ minutes and went away within 5 minutes. In the second experiment blocking of the inhibitory fibres to the heart with atropine did not alter the findings.

Influence of the inhibitory mechanism of the heart over the changes and irregularities in the heart beat after the injection of bismuth.

This point was considered in four of the experiments.

In Experiment No. 11, on a dog, a dose of atropine sufficient to provent slowing of the heart rate on stimulation of the vagus nerve was given. A small dose of bismuth then slowed the heart to the same extent as did a like dose before the injection of atropine. There were likewise no changes in the degree or type of alteration in the amplitude of the beats after atropine. When a larger dose of bismuth was given in this experiment, the irregularities and changes seen were similar to those in unatropinised animals.

In Experiments Nos. 3 and 4, the cats used were decapitated. The slowing of the heart rate and other changes which occurred after bismuth injections were similar to those in other experiments.

Experiment No. 5 on a vagotomised cat showed changes similar in extent and degree to those in animals where the vagi were not divided.

From the analysis of these experiments, the result of which analysis has been recorded briefly above/

above, I conclude that the inhibitory mechanism of the heart takes no part in the changes observed in the various stages of the action of bismuth on the heart.

But an alteration in the response of the heart to stimulation of the vagus nerve was noted after the injection of bismuth. In Experiment No. 7 on a dog, using the minimum strength of current which produced slight slowing in the beginning of the experiment, there were obtained marked slowing and stoppage of the heart on stimulation of the vagus during the irregularities. This is due to the fact that any lengthening of conduction such as occurs on stimulation of the vagus will have more effect if conduction is already impaired, as it is to a considerable extent in the heart block in bismuth poisoned animals.

Electrocardiographic Experiments.

A description of the procedure and technique of these experiments has been given already. It will be my endeavour in the following pages not to give any detailed account of the results, but rather to corroborate the findings of the kymographic experiments and describe more fully several points which are illustrated more clearly by electrocardiograms.

In the preceding chapter it will have been seen that pronounced cardiac irregularity can be brought about with ease by the intravenous injection of bismuth. These changes are shown well in the kymographic experiments whereas electrocardiograms show,rather,the mode of onset of these irregularities. I have already stated that artificial respiration was not carried out during the electrocardiographic experiments, in contradistinction to the others. When the heart became very irregular, therefore, an element of asphyxia took part in the proceedings and as asyphxia may itself be responsible for cardiac irregularity, electrocardiograms of these marked changes are unreliable and but few of them have been inserted. Sinus arrhythmia is of common occurrence and is marked in dogs; in most cases therefore the animals used were atropinised before the experiments were carried out. The most prominent changes will be described first.

1. /

1. Alterations in Conductivity.

(a) Alterations in the P-R interval.

Considerable lengthening of the time of conduction between the auricle and ventricle was a prominent accompaniment of the missed beats and heart block noted in the kymographic experiments. But electrocardiograms show that lengthening of this interval may occur and does occur before these irregularities in rhythm become manifest. The following tracings illustrate this:

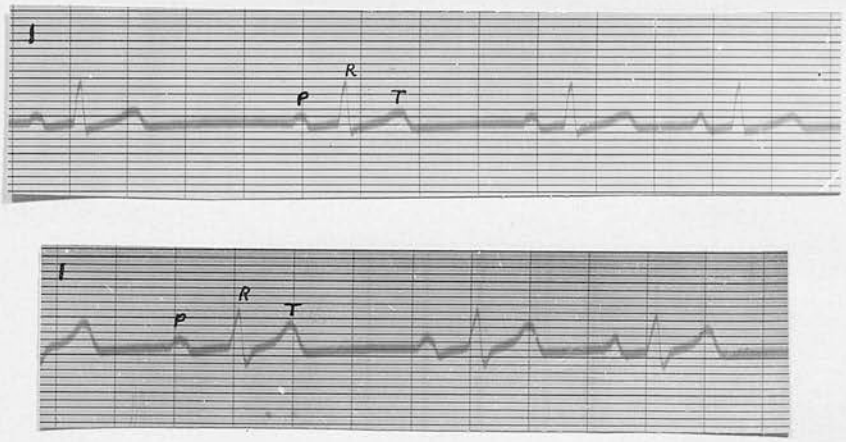


Figure 12.

Electrocardiograms from lead 1 in a dog before and after 0.54 mgs. bismuth metal per kilo. The P-R interval in the first tracing is .13 seconds and in the second tracing, which was taken two minutes after the injection, it is .18 seconds. The duration of the ventricular complex is lengthened after the injection. Some respiratory irregularity is present. (Time in $\frac{1}{5}$ second)

Figures 13 and 14 /

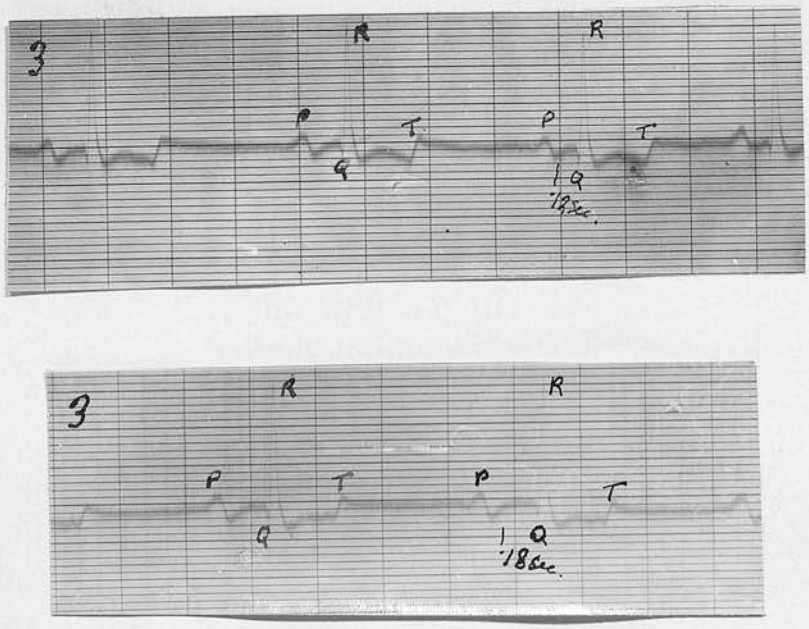


Figure 13.

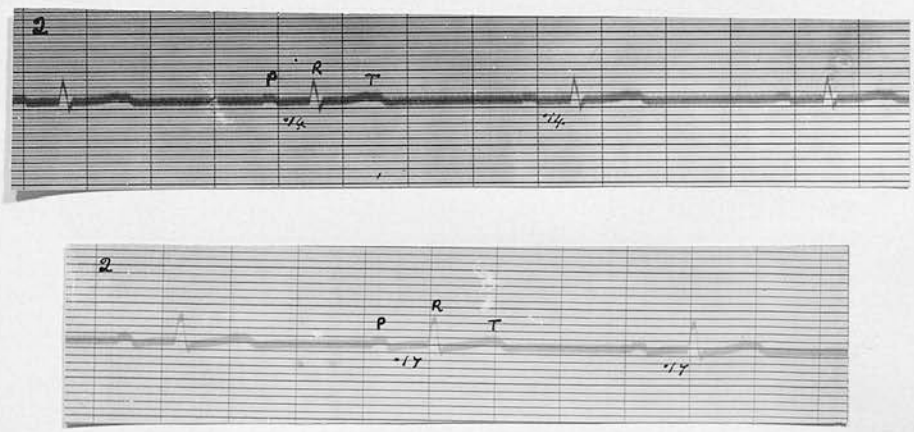


Figure 14.

Figures 13 and 14.

Electrocardiograms from two dogs before and two minutes after an injection of 0.45 mgs. bismuth metal per kilo. each, showing changes in P-R intervals. (Time in $\frac{1}{5}$ seconds).

It will be seen from the above tracings that a lengthening of the P-R interval can occur after very small doses of the metal and that it becomes clearly demonstrable/

demonstrable before other changes occur. The lengthening remains and even becomes more marked when changes in the ventricular complex or irregularities come on.

(b) Alterations in the duration of the ventricular complex.

A lengthened duration of the ventricular complex was a constant accompaniment of pronounced increases in the P-R interval. In the above tracings slight increases in the ventricular complexes may be seen. Below is given an example of a marked increase, a phenomenon commonly observed.

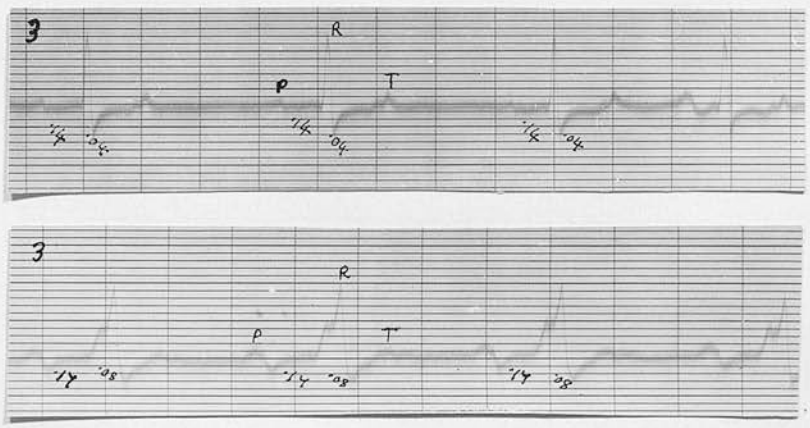


Figure 15.

Electrocardiograms from a dog before and three minutes after 0.54 mgs. bismuth metal per kilo. Increases in the P-R intervals and duration of the ventricular complexes are seen. There is some respiratory irregularity in the first tracing. (Time in $\frac{1}{5}$ seconds).

Figure 16. /

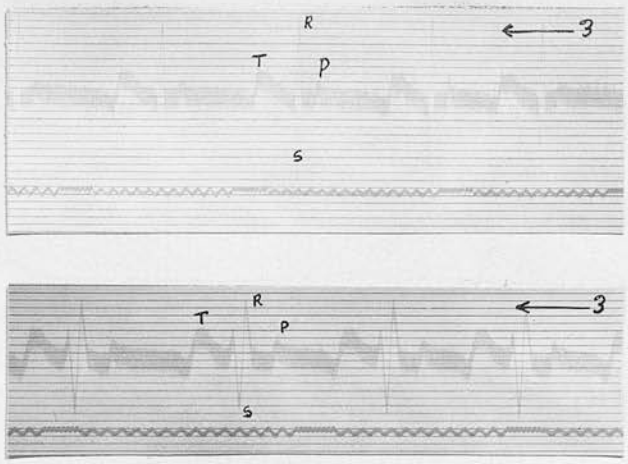


Figure 16.

Electrocardiograms from lead 3 from a dog before and after 0.67 mgs. bismuth metal per kilo. An increase in the P-R interval and increased duration of the ventricular beat are seen. The tracings read from right to left. The plate was moving at the same rate in the two tracings. (Time in 1 sec.).

More marked changes in the duration of the ventricular complex were accompanied by definite evidence of abnormal spread of the excitation wave in the ventricles. This is discussed under the following heading:

(c) Aberration of the ventricular distribution of the excitation wave.

This was a commonly observed occurrence. Various degrees of aberration were met with, from those of slight extent to definite bundle branch block. Lengthening of the P-R interval and slowing of the heart rate always occurred before the change in type of the ventricular beat was evident. A few examples of the various types are given below. The small oscillations which are present in some of the following/

ing tracings are mechanical effects.

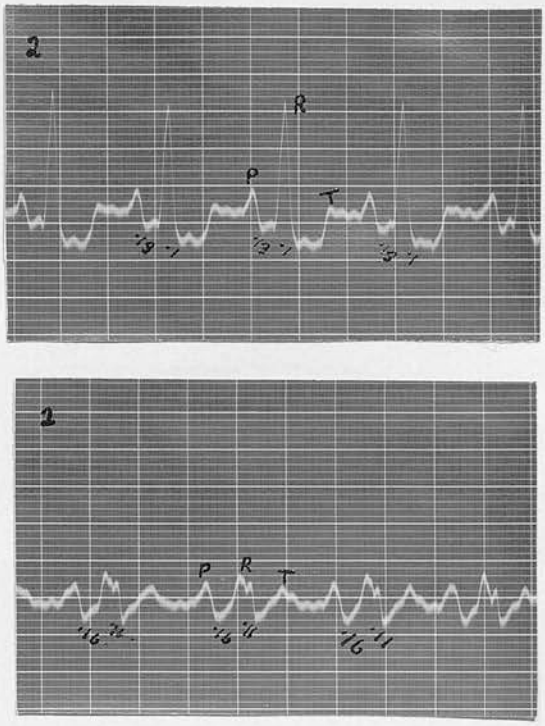


Figure 17.

Electrocardiograms (lead 2) from a dog before and after 1.08 mgs. bismuth metal per kilo. There is lengthening of the P-R interval and increased duration of the ventricular complex. The change in form of the ventricular complex denotes aberration of the ventricular excitation wave. (Time in $\frac{1}{5}$ sec.).

Figure 18. /

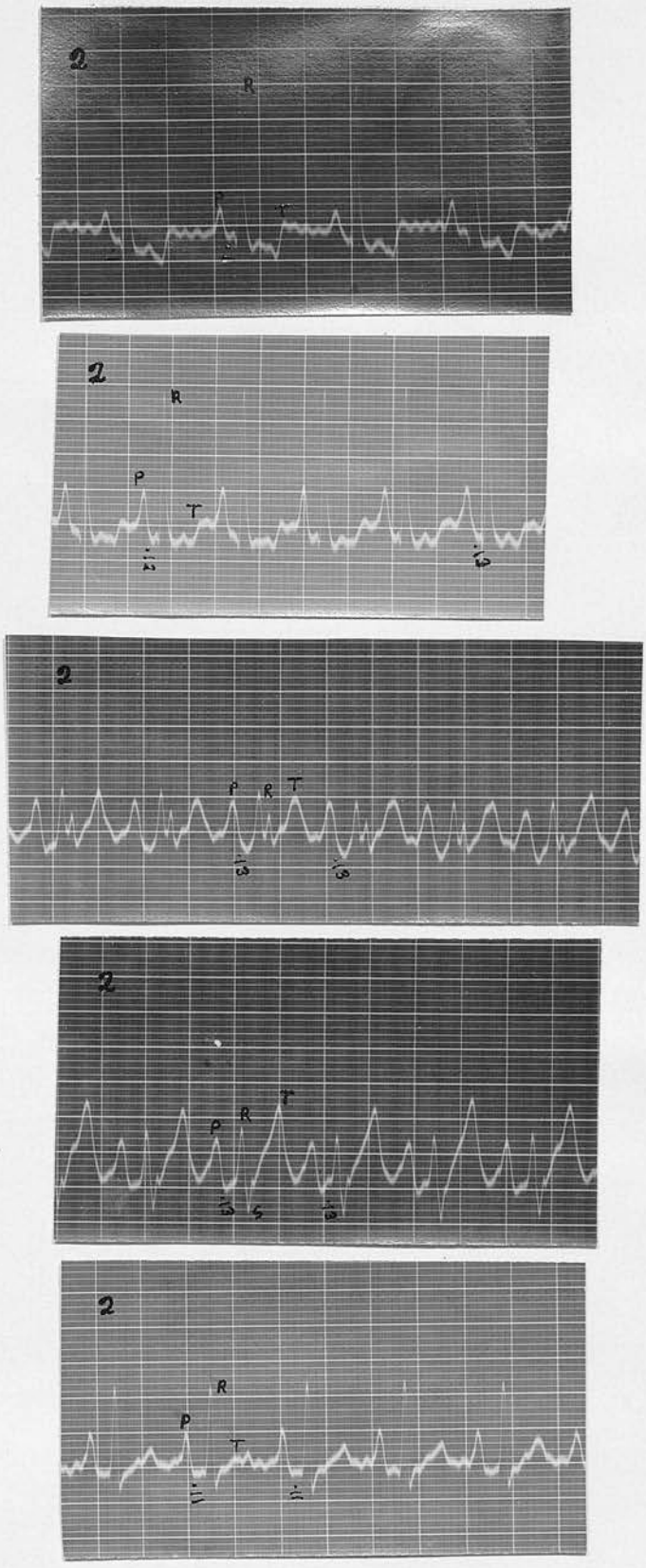


Figure 18.

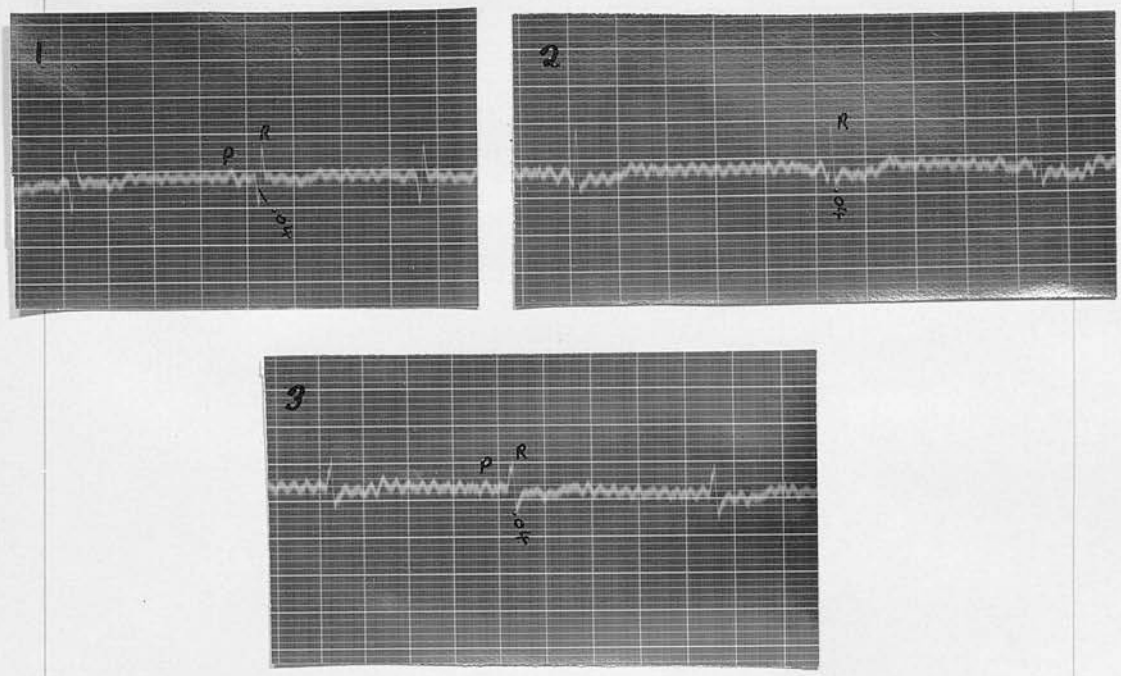
Electrocardiograms (lead 2) from a dog before and at 1 minute intervals after a dose of 1.08 mgs. bismuth metal per kilo. The fifth tracing was taken/

taken half an hour after the injection and shows recovery. In the second tracing there is an increase in the P-R interval. In the third tracing there is, in addition to the increase in the P-R interval, aberration of the ventricular excitation wave with increased duration of the ventricular complex. In the fourth tracing the aberration becomes more marked and the T wave is greatly increased in height and duration. In the fifth tracing the heart has recovered a normal type of ventricular complex but it still shows some slowing of the rate. (Time in $\frac{1}{5}$ sec.)

The abnormalities in the path of the ventricular excitation wave need not be very marked to produce the changes in the above tracings. But a more marked form of aberration was observed, a form where it could be said that one of the bundle branches was involved. Two examples of this more definite type will be given.

Figure 19. /

Figure 19.



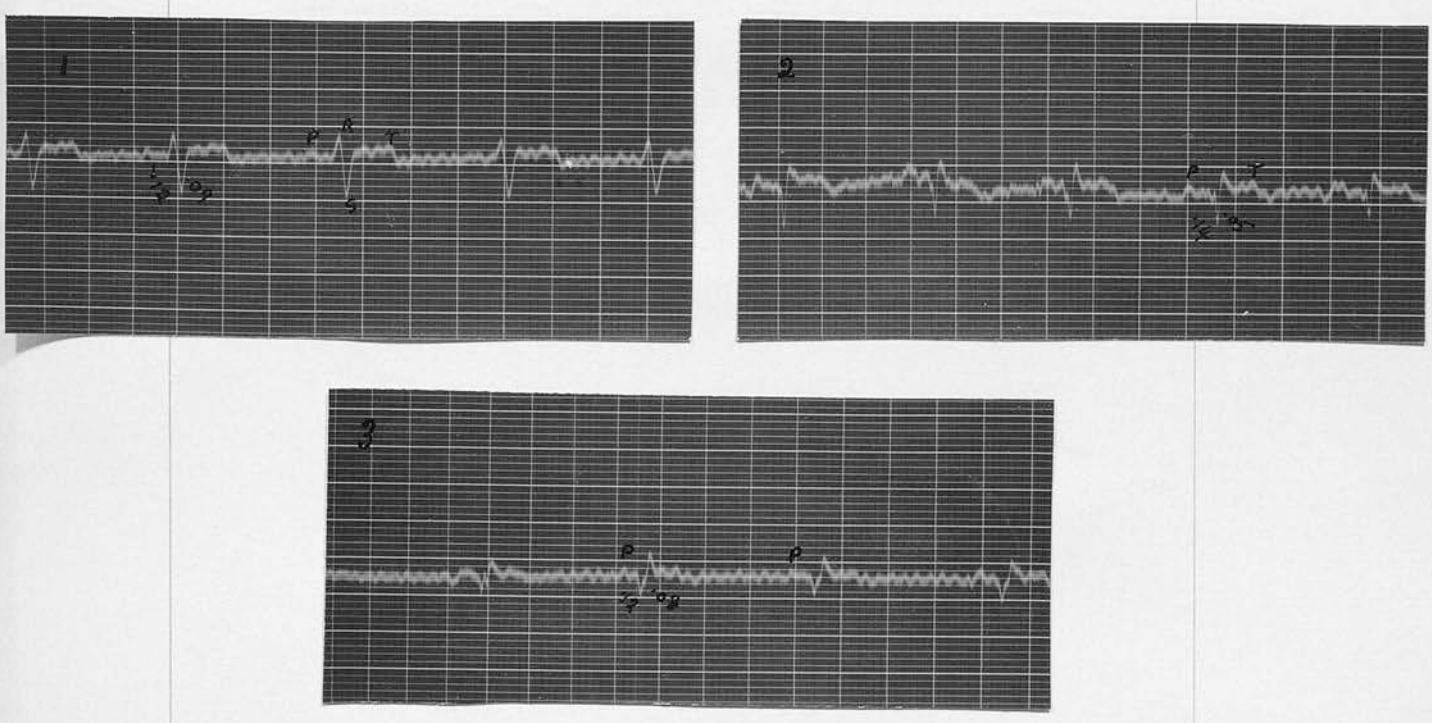
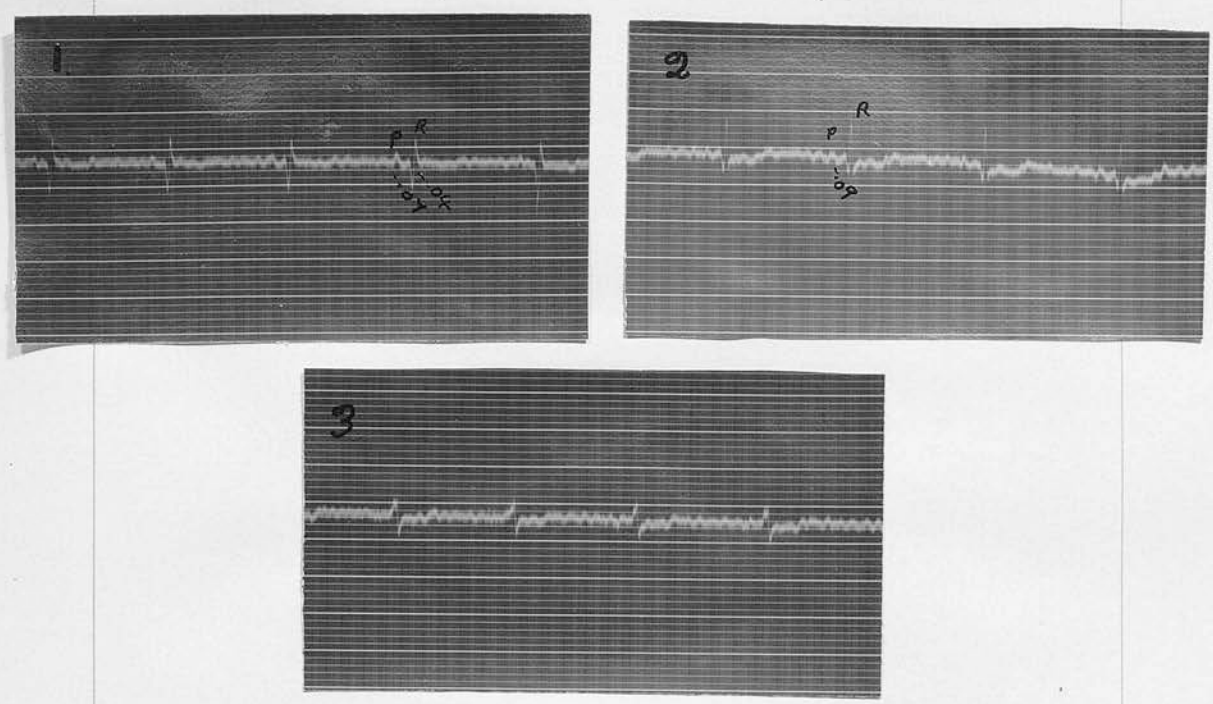


Figure 19 (Contd.).



Electrocardiograms from the three leads in a dog before, three minutes after, and half an hour after 0.99 mgs. bismuth metal per kilo. The P waves in the tracings taken before the injection are not clearly seen so that no measurements of the P-R intervals have been made in them.

In the second series of tracings the ventricular complex has changed in type and is of longer duration. These changes denote a lesion in the right bundle branch.

The third series show recovery of the heart half an hour later. (Time in $\frac{1}{5}$ sec.)

Figure 20. /

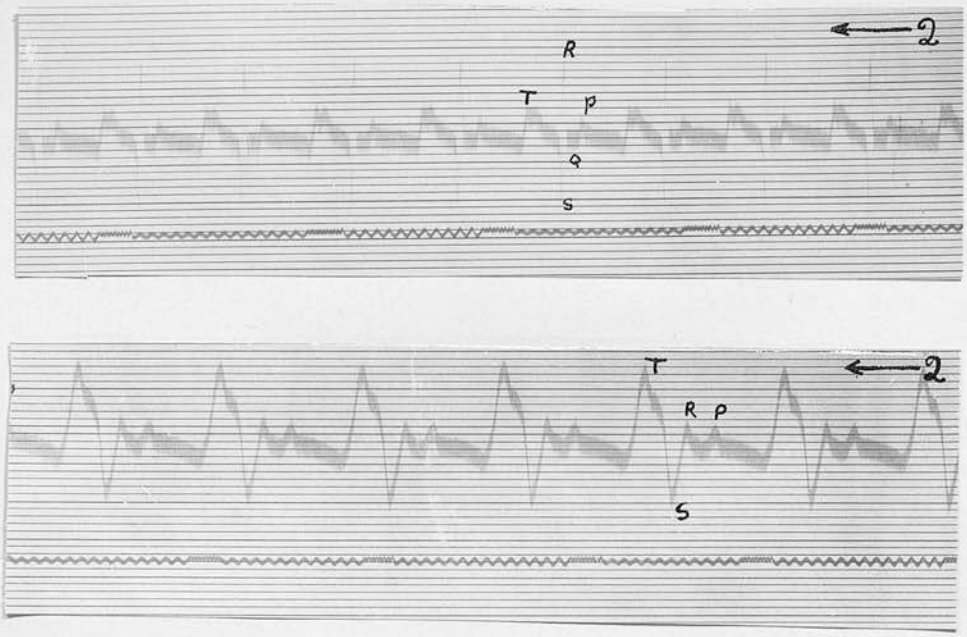


Figure 20.

Electrocardiograms from lead 2 from a dog before and immediately after 1.12 mgs. bismuth metal per kilo. There are lengthening of the P-R interval, changed type and lengthened duration of the ventricular complex. These changes point to a right bundle branch lesion. Electrocardiograms taken half an hour later showed a normal type of ventricular complex. The tracings read from right to left. (Time in 1 sec. intervals).

2. Irregularities in rhythm in electrocardiographic experiments.

The changes in the P-R interval and the ventricular complex having been discussed, a short description of the irregularities in rhythm superimposed on these changes will be given. For reasons given before, the irregularities which were accompanied by marked embarrassment of the heart will/

will not be described here. The irregularities were of only temporary duration, the heart either quickly recovering or going on to more marked irregularity and then recovering, or not, according to the amount of bismuth salt injected. Tracings which illustrate the various changes observed are described below.

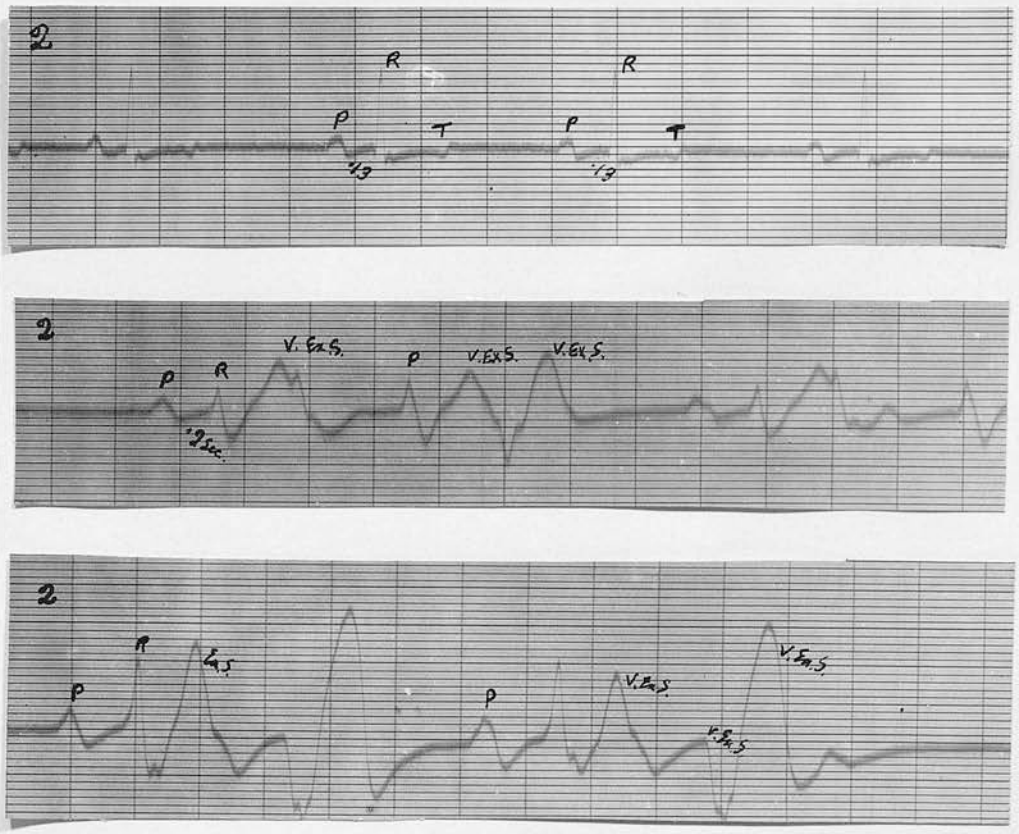


Figure 21.

Electrocardiograms from a dog before and after 1.6 mgs. bismuth metal per kilo. In the second tracing each ventricular beat occurs after a long P-R interval. After each ventricular beat there occur ventricular extrasystoles which originate from different parts of the ventricle. In the third tracing each ventricular movement is followed by two extrasystoles, the first originating in the right ventricle /

ventricle and the second in the left ventricle. In this experiment the heart recovered a normal rhythm within an hour. (Time in $\frac{1}{5}$ sec.).

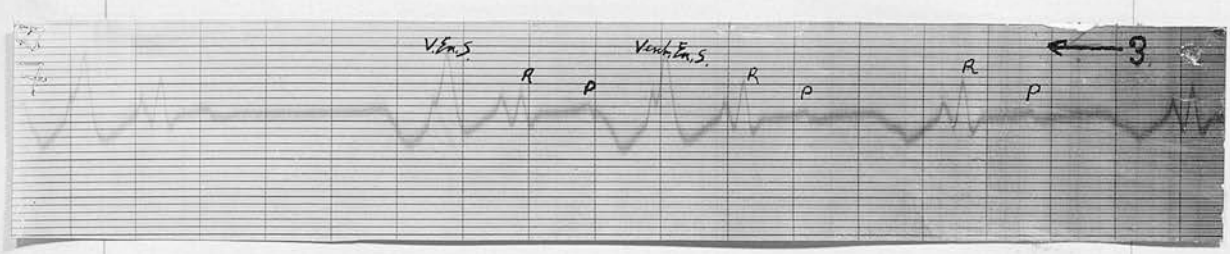


Figure 22.

Electrocardiogram from lead 3 from a dog immediately after 1.53 mgs. bismuth metal per kilo. The irregularity became more marked a few minutes later and the rhythm was apparently normal an hour after the injection. The tracing reads from right to left. There is in the later part of the tracing a coupled rhythm due to each ventricular beat being followed by an extrasystole originating in the right ventricle. After the fourth beat there is a missed ventricular beat. (Time in $\frac{1}{5}$ sec.).

Figure 23 /

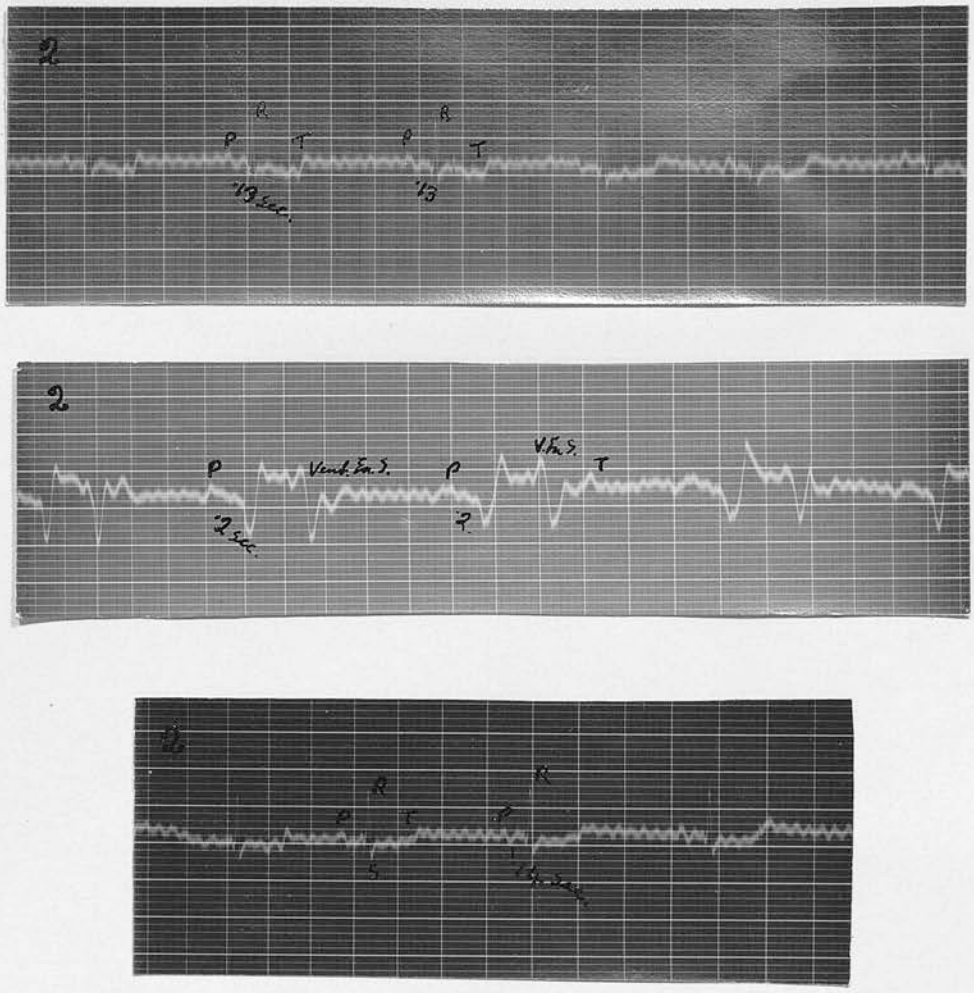


Figure 23.

Electrocardiograms (lead 2) from a dog before and after an injection of 0.9 mgs. bismuth metal per kilo. The second electrocardiogram was taken two minutes after the injection and shows coupled ventricular beats. The first beat of each couple is preceded by a P wave and is aberrant. The second beat is apparently a ventricular extrasystole. The third tracing shows the recovery of the normal rhythm 20 minutes later. (Time in $\frac{1}{5}$ sec.).

Figure 24. /

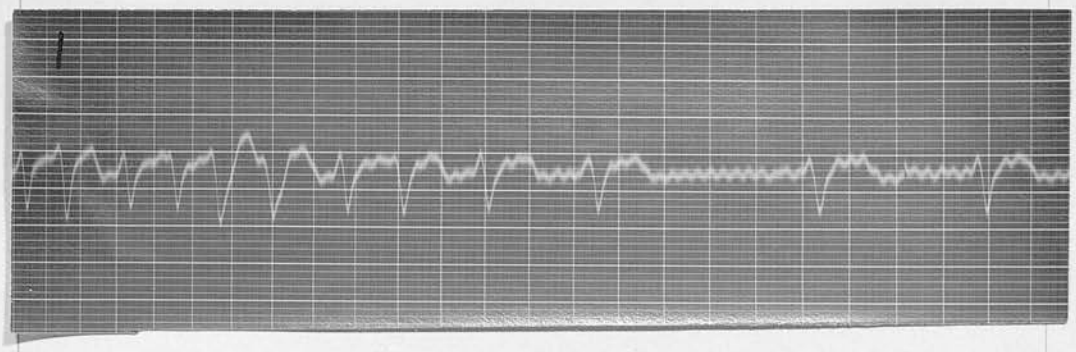


Figure 24.

Electrocardiogram from lead 1 from the same dog as the above series but after a second injection of 0.9 mgs. bismuth metal per kilo. There is in the left part of the tracing a tachycardia of ventricular origin, but this passes off and the heart beats at almost the same rate as before the injection, the beats apparently being ventricular extrasystoles and not being preceded by P waves. In this experiment a normal rhythm was present half an hour after the injection. (Time in $\frac{1}{5}$ sec.).

Death of the Heart /

Death of the Heart.

In the records of the experiments and in the discussion which follows, it will have been noted that marked cardiac irregularities follow the intravenous injection of small doses of the soluble salts of bismuth. If fatal doses were given, very marked changes in the heart were noted, followed in a few seconds' time by stopping of the heart. There was no order in the manner in which the heart stopped, and indeed it was found difficult to produce permanent stopping. The changes noted before death of the heart were:- A more marked slowing of the rate of the auricle, marked lessening of systole of the auricle and the ventricle and increase of diastole of the ventricle. Heart block became more complete, even to a 6-1 or 7-1 block. Lengthening of the duration of the beat and of the A-V interval were marked. The ventricle usually stopped abruptly in diastole and before the auricle as in the following tracing.

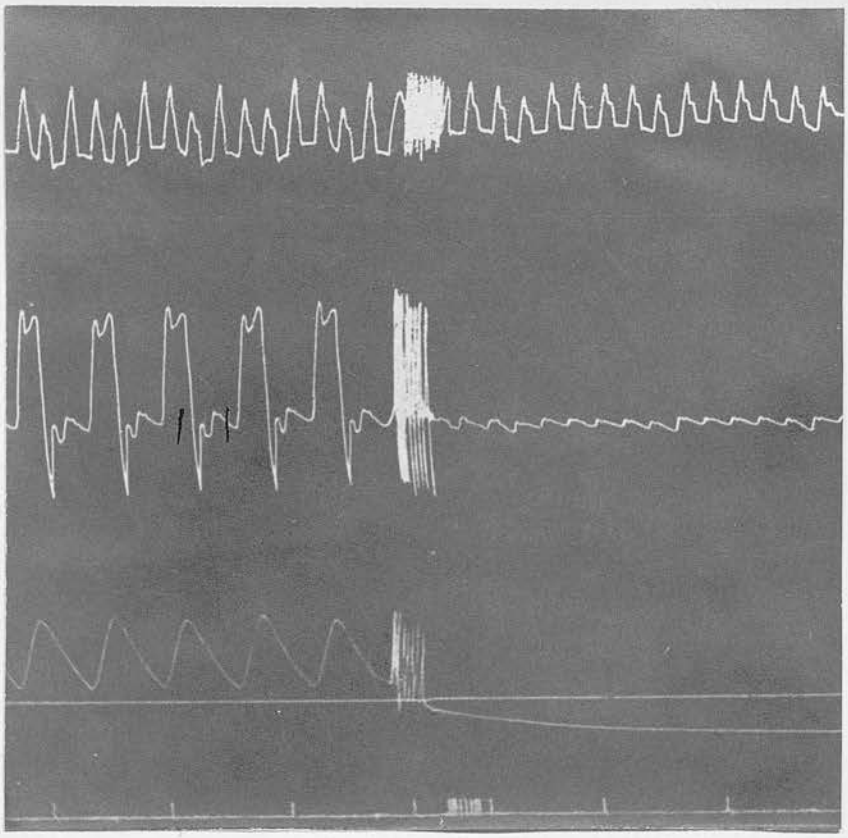


Figure 25.

Tracing from a cat (Experiment No. 2) after 5.8 mgs. bismuth metal have been run into a vein. Auricle (upper), ventricle (lower). The ventricle stops in diastole; the auricle continues to beat weakly for a few seconds and then stops. When the heart stops, the blood pressure falls to the base line. (Time in 2 second intervals).

The auricle and ventricle may also undergo a course fibrillation before stopping in diastole as shown in the next tracing.

Figure 26. /

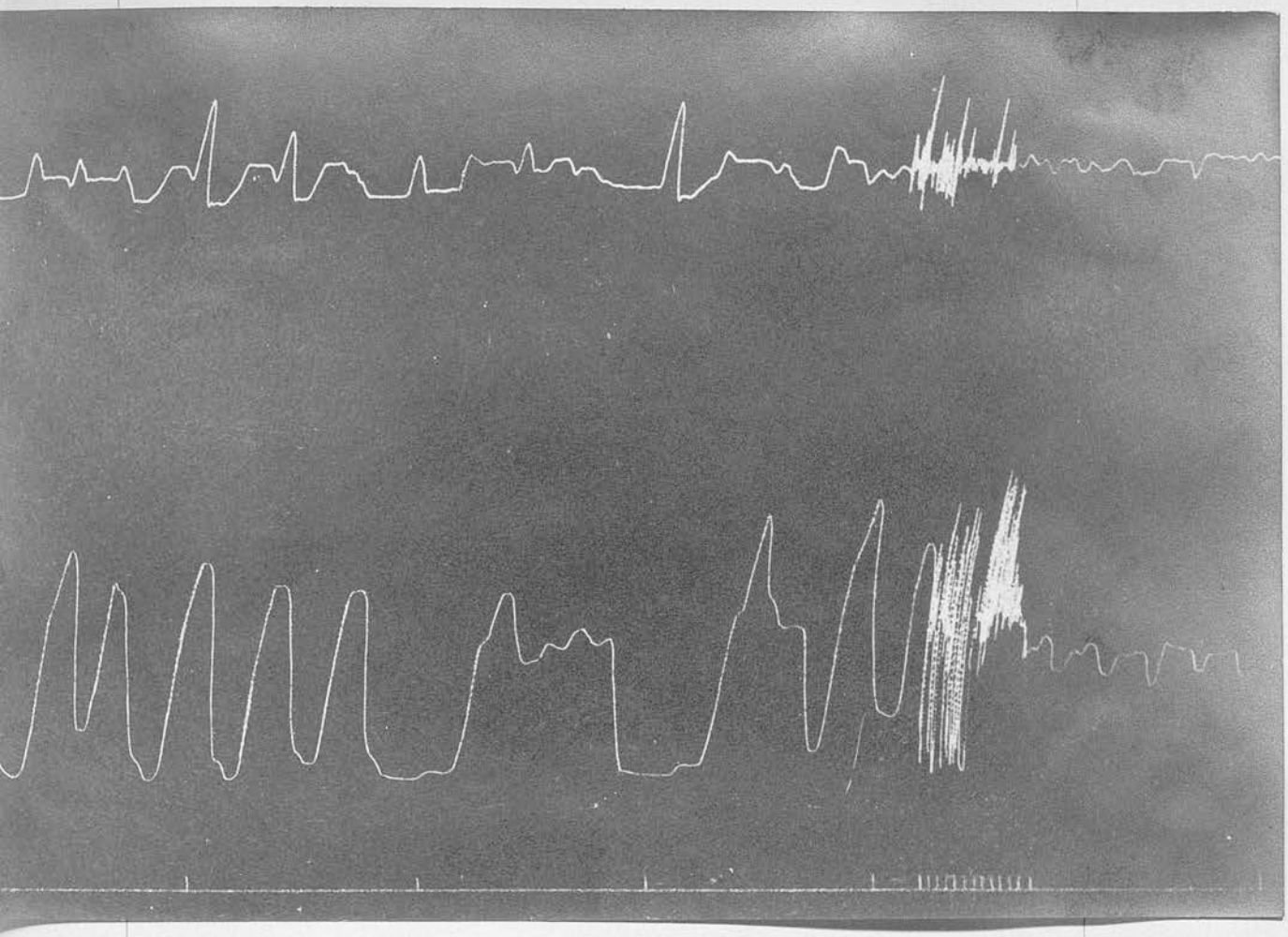
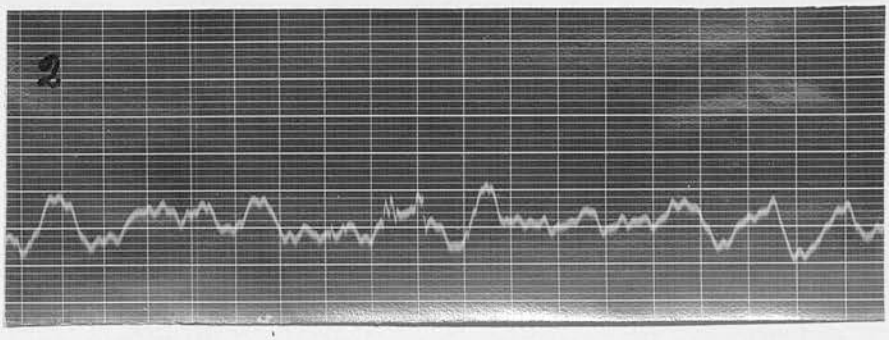


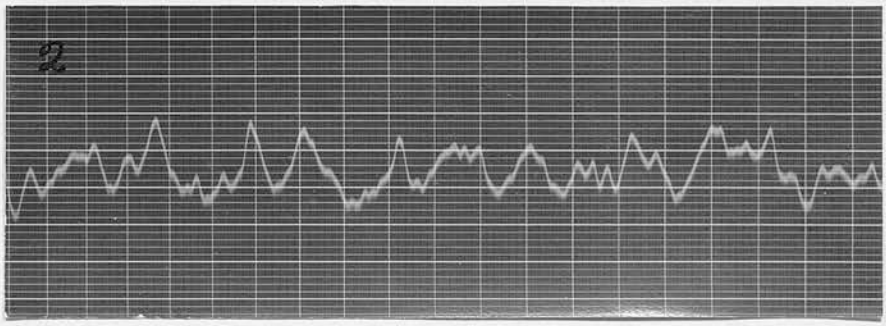
Figure 26.

Myocardiograms from a dog (Experiment No. 7) after the injection of 4.2 mgs. bismuth metal per kilo Auricle (upper), ventricle (lower). For a time the heart is very irregular, then a course fibrillation of the auricle and ventricle come on and the heart stops later in diastole. (Time in 2 sec. intervals).

Fibrillation was never a common occurrence in the kymographic experiments unless the metal was injected quickly in large doses. It was rather more common in the electrocardiographic experiments which showed evidence of ventricular fibrillation after all evidence of heart movement to the palpitating hand had gone/

gone.





Figures 27 and 28 .

Two electrocardiograms from lead 2 from two dogs after they had received an injection of 2.6 mgs. bismuth metal per kilo each. There is marked irregularity in the tracings, a state which denotes ventricular fibrillation. (Time in $\frac{1}{5}$ sec.)

Figure 29 . /

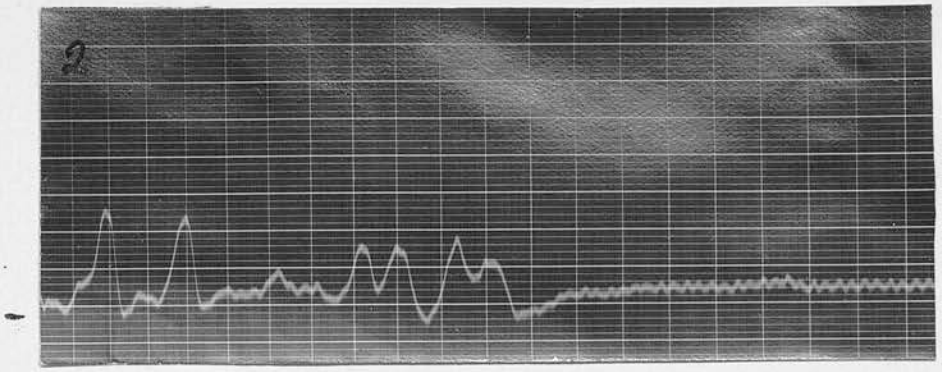


Figure 29.

Electrocardiogram from lead 2 from a dog five minutes after an injection of 2.5 mgs. bismuth metal per kilo. The heart stops beating after a short period of ventricular fibrillation. Ventricular fibrillation in not present at the beginning of the tracing. (Time in $\frac{1}{5}$ sec.).

Reversibility of the action of bismuth on the heart.

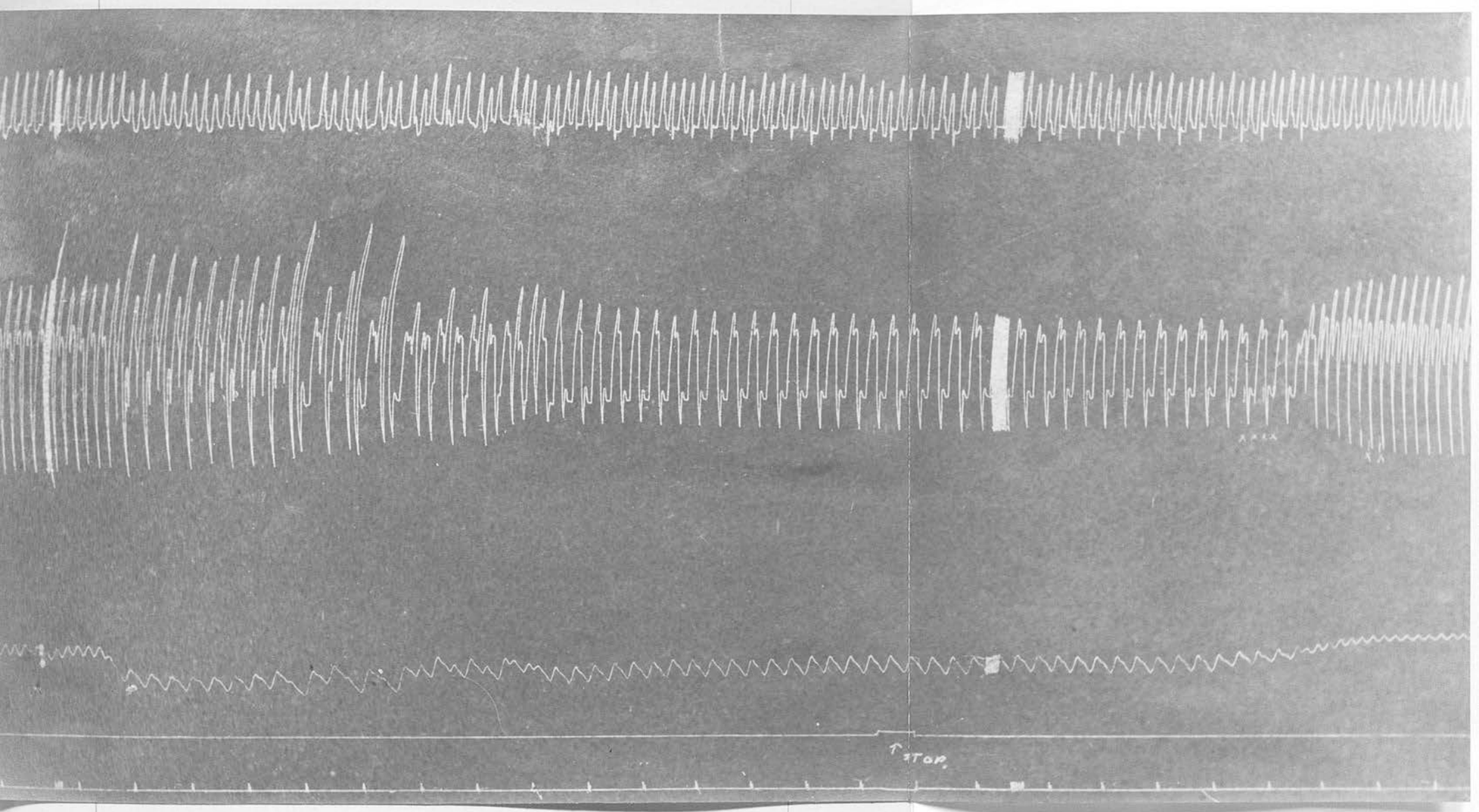
An interesting phenomenon noticed in nearly all the experiments both kymographic and electrocardiographic was the ease with which the heart recovered after small doses of bismuth. Even after large doses this was noticed sometimes, recovery taking place even after the heart had stopped for a number of seconds.

Recovery from the slight effects took place easily and completely within five minutes. Recovery from the later irregularities took place and was complete if the infusion of bismuth was stopped. Recovery from the marked types of heart block,naturally, took a longer time, but did occur if the heart was not severely injured.

During/

During recovery, irregularities belonging to the second stage were often noticed before the rhythm became regular. Again, while the rhythm found no great difficulty in becoming regular, the amplitudes of the auricle and ventricle recovered only a part of their former strength and most of the increased diastole which occurred, remained. Electrocardiograms have been shown already where the heart recovered after slight changes, but examples will be given here of the recovery which may occur after marked irregularity.

Figure 30 /



(Figure reduced by one-third)
Figure 30. (From Experiment No. 5).

Tracings from auricle (upper), ventricle (lower) and the blood pressure from a cat after 3.2 mgs. bismuth metal had been run into a vein. The infusion is stopped at the mark on the tracing. There is onset of 2-1 heart block after a short phase of extra-systolic/

systolic irregularity. When the infusion is stopped the ventricle rapidly recovers its normal rhythm and part of its normal amplitude. The blood pressure also regains its normal height. (Time in 10 sec. intervals).

If a dose of bismuth be injected rapidly into the blood stream, the heart stops in diastole for a varying period of time and then recovers. This is a very interesting phenomenon and was observed repeatedly. The following tracing is a typical example:

Figure 31 /

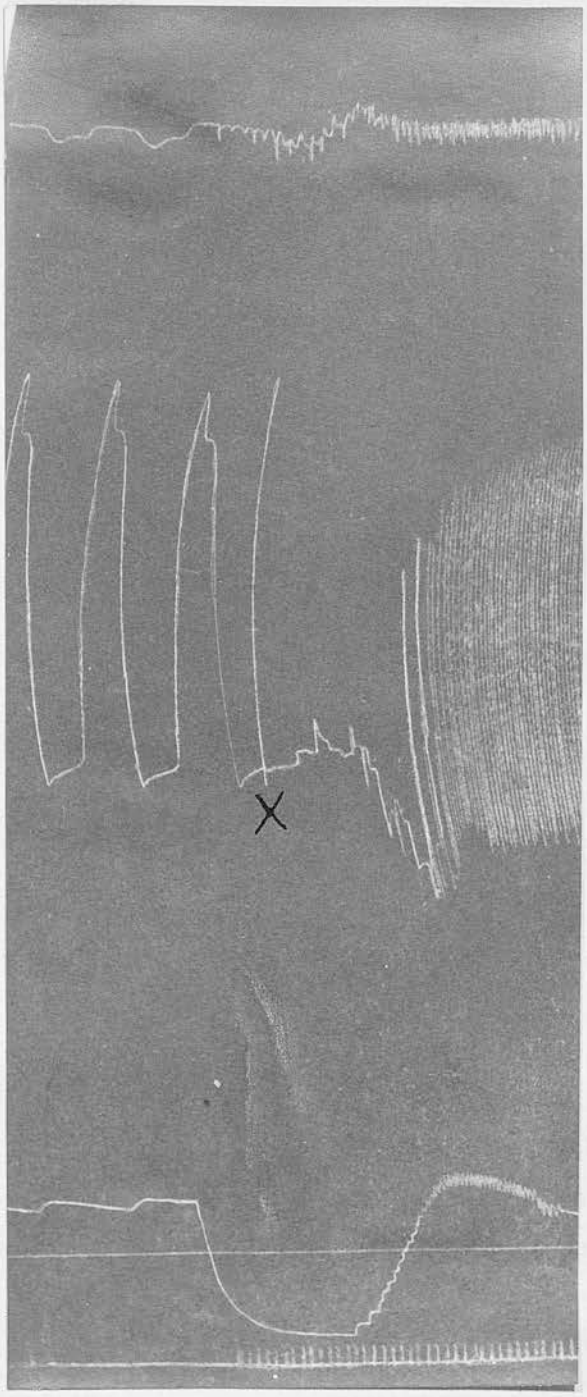


Figure 31.

Tracings from auricle (upper), ventricle (lower) and blood pressure from a cat 30 seconds after 3.2 mgs. bismuth metal have been injected quickly into a vein. At X the drum was moved at a slower rate.

The/

The auricle has stopped beating, the slight movements of the lever being mechanical. The ventricle, after a preliminary stage of heart block, stops in diastole and then slowly recovers. The blood pressure falls to the base line and then rises as the heart improves. (Time in 2 sec. intervals)

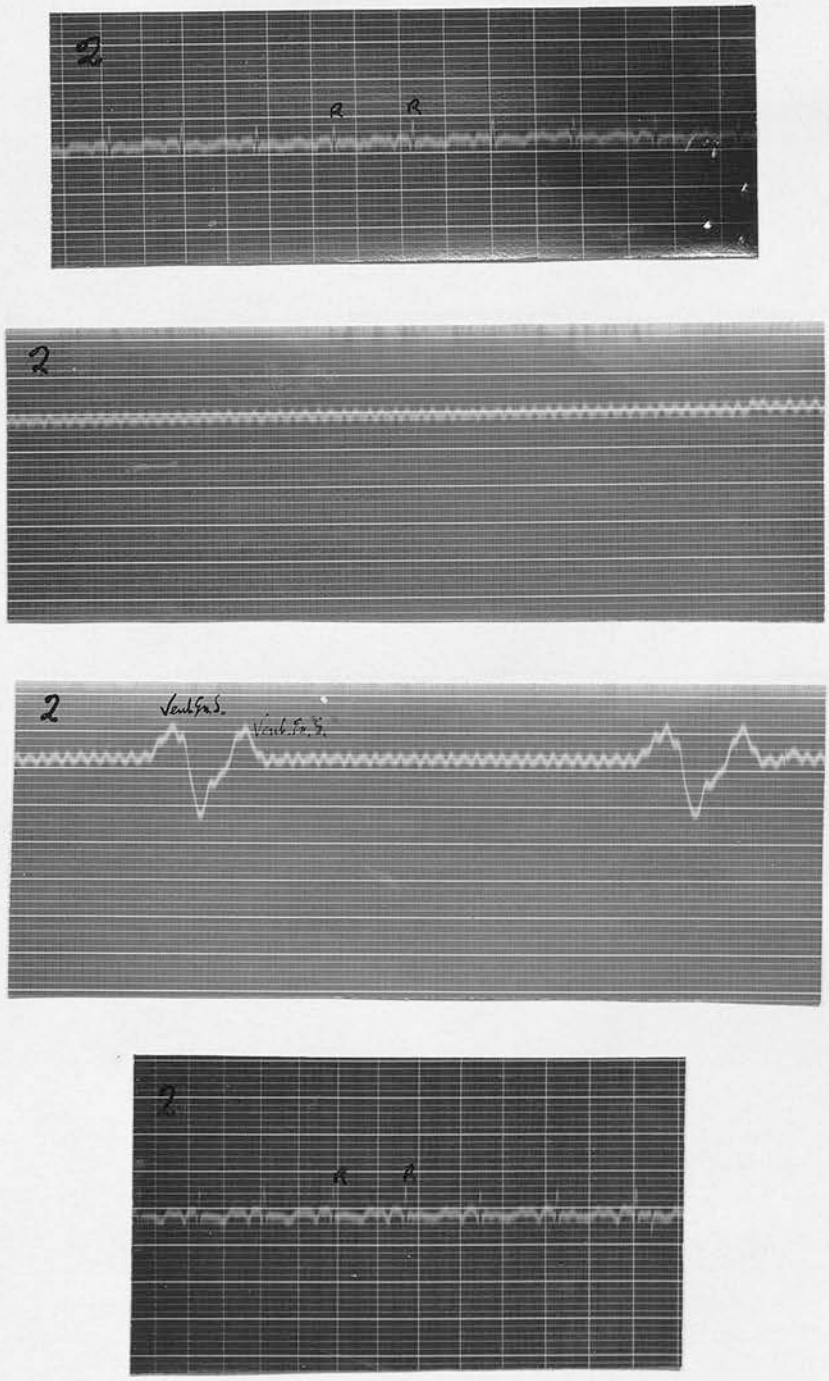


Figure 32.

Electrocardiograms from a cat (lead 2) after a dose/

dose of 2.1 mgs. bismuth metal had been injected rapidly into a vein. The first tracing is from the normal heart. The second tracing was taken immediately after the injection and shows that the heart has stopped beating. The third tracing was taken three minutes later and shows partial recovery of the heart beat. The beats are composed of two extrasystoles occurring together, the first arising in the right ventricle and the second in the left ventricle. The fourth tracing shows the state of the heart 25 mins. later. There is recovery of normal rhythm. (Time in $\frac{1}{5}$ sec.).

The above tracings are merely examples of the marked reversibility of the action of bismuth on the heart. They demonstrate what was one of the most evident findings in the experiments, namely, that the heart could recover rapidly after injections of bismuth if the amount given was not too large.

CONCLUSIONS /

CONCLUSIONS AS TO THE RELATION BETWEEN DOSE AND EFFECT ON THE CIRCULATORY SYSTEM.

A short chapter here will classify much that would be of little use if interspersed throughout the preceding account.

The doses are stated in terms of milligrams of bismuth metal per kilo. injected, of course, in the form of bismuth sodium tartrate; the small doses mentioned were in all cases the first injections in the experiments, and the injections have been made over approximately the same length of time. From the manner in which the experiments were conducted, nearly all the large doses followed on a previous smaller one and thus the relation with them between dose and effect is not strictly accurate.

Minimum and maximum doses which produced changes in the heart and blood pressure.

0.45 to 0.54 mgs. bismuth metal per kilo. gave a slight fall in blood pressure and lessening of the amplitude, and slowing, of the heart.

1.34 to 1.78 mgs. bismuth metal per kilo. gave a marked fall in blood pressure and marked lessening of amplitude, irregularity and slowing of the heart, and if repeated in the course of the experiment, gave more pronounced slowing, lessening of amplitude and death of the heart.

2.67 /

2.67 mgs. bismuth metal per kilo. gave marked irregularity, lessening of amplitude and temporary stopping of the heart.

Reference to the determination of the lethal dose of bismuth in cats shows that the minimum fatal dose is ten times the minimum dose which gives slight changes in the heart and blood pressure.

Discussion on the changes in the heart.

An attempt will be made in this chapter to explain the various changes in the heart rate and rhythm noted in the above experiments, on the basis of disturbance of the functions of the heart muscle. The alterations which require explanation are:

(1) Slowing of the heart rate.
(2) Lessened amplitude and lessened systole of the auricle and ventricle.
(3) Increased diastole of the ventricle.
(4) Lengthening of period of auriculo-ventricular conduction.
(5) Lengthening of duration of the ventricular beat.
(6) Occurrence of missed beats and heart block.
(7) Occurrence of ventricular extrasystoles.
(8) Occurrence of alternation of the ventricular amplitudes.

Such a variety of changes must be due to a disturbance of more than one of the functions of the heart muscle. The five fundamental functions of heart muscle set out by Gaskell are: Stimulus production, excitability, conductivity, contractility and tonicity. It is proposed to show here how these functions are altered in heart muscle poisoned with bismuth and how their alteration accounts for the above-mentioned list of changes.

(a) Stimulus production.

This function is responsible for the regulation of the rate of the heart, and its depression would lead to slowing. The slowing noted after the injection of bismuth has been shown to be unaffected by paralysis of/

of the inhibitory mechanism and must therefore be the result of depression of stimulus production at the sinus part of the auricle.

(2) Excitability.

I use the term excitability in its limited sense, that is, the sensitivity of the heart muscle to electrical shocks. Such a measure of the sensitivity of the heart muscle cannot act as a comparable guide to the sensitivity of the muscle to impulses born intrinsically. But inasmuch as there is no way of measuring this latter, and extrasystoles arising from mechanical stimuli are similar in nature to those arising from natural impulses, it may be assumed that the excitability of the muscle to shocks gives some index to the causes of the extrasystoles and the heart block which were observed.

It was shown in Figures 10 & 11 which were taken from experiments where the excitability of the muscle was tested by electrical shocks, that this function was markedly depressed after the injection of bismuth. It is very probable that such depression plays a part in the onset of the heart block observed so often in the experiments, because the poisoned muscle cannot respond so readily to impulses from the auricle. But, as is explained below, impairment of the other functions occurs to a marked degree, is more easily and more accurately measured, and is probably of greater importance in the production of the heart block than the lessened excitability. It is understandable that extrasystoles are liable to occur in heart/

heart muscle if conductivity is impaired to a greater extent than excitability, because when the natural impulse to the ventricle is delayed abnormal impulses have more opportunity to develop. Thus lessening of excitability to a certain extent is not incompatible with the occurrence of ventricular extrasystoles.

(3) Conductivity.

Two types of disturbance of this function were noted, one, where the interval between the auricular and the ventricular beats was lengthened, and the other where the stimulus of contraction passed more slowly from fibre to fibre in the ventricular muscle. These two types usually occurred together in the experiments but not always to the same degree. The first type, that is, the auriculo-ventricular conduction, was manifested by an increase in the A-V interval in the kymographic experiments and by an increase in the P-R interval in the electrocardiographic experiments. The second type, where the passage of the impulse from fibre to fibre in the muscle of the ventricle, was slowed, was shown by an increase in the duration of the ventricular beat in both sets of experiments. In addition, the electrocardiographic experiments showed that in the majority of cases the increase in the duration of the ventricular beats was due partly to an abnormal passage of the ventricular excitation wave and not altogether, as might be inferred from the kymographic experiments, to a slower passage of a normal excitation wave. In other words, they showed that/

that aberration of the wave in the ventricle was an additional factor to the delayed conduction in the tracts and muscle.

Lengthening of the A-V or P-R interval.

The fact that increases in duration of this interval occur with ease after small doses of bismuth has been stressed before. It is easy to understand how such a delay in conduction could cause heart block or missed beats and, indeed, this delay must be an important factor in their onset.

Aberration in the ventricular excitation wave and depressed conduction from fibre to fibre in the ventricle.

These abnormalities give rise to increased duration of the ventricular beat. This sometimes may occur to such an extent that the next auricular impulse falls on an incompletely relaxed ventricle and thus either fails to give rise to a contraction or gives rise to an abortive beat. Thus it plays some part in the occurrence of missed beats and heart block.

When the increase of the duration of the ventricular beat was marked one could see by direct observation of the heart that the wave of contraction in the ventricle passed comparatively slowly over the muscle, usually following some definite path. Occasionally the path of travel of the impulse would change and this gave rise to either a lessening or increase of the amplitude of the ventricle. Such a state is shown in the following tracing. The heart

was/

was being watched when the change took place and the phenomenon above described was clearly seen.

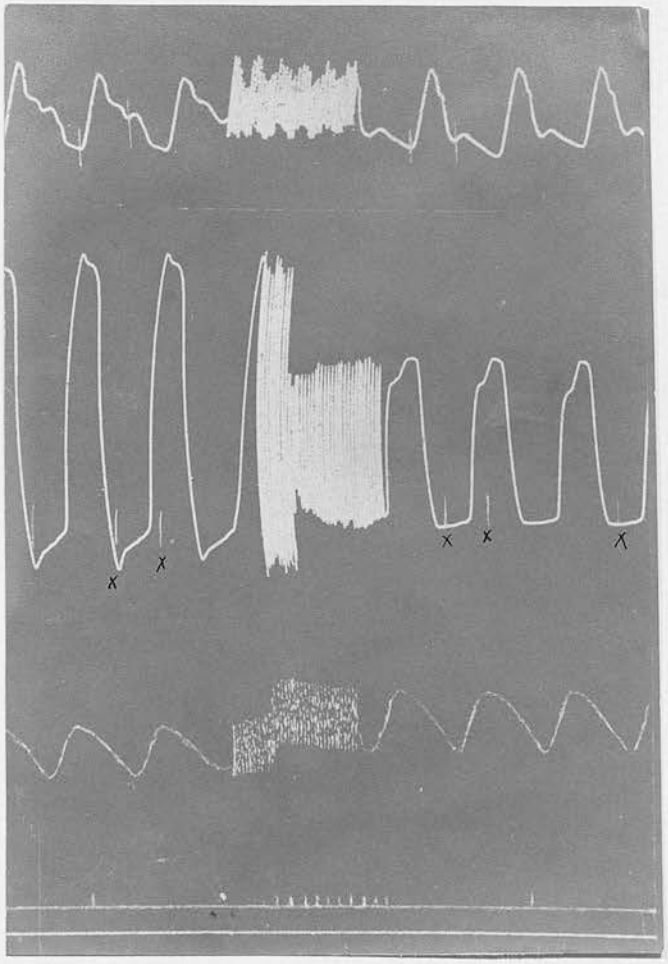


Figure 33.

Tracings from auricle (upper), ventricle(lower) and a blood pressure tracing from a cat (Expt. 10) after 3 mgs. bismuth metal per kilo. There is 2-1heart block present. Every second auricular movement is partly obscured by a mechanical effect from the ventricle. In the middle of the tracing the amplitude of the ventricular contraction changes abruptly. As stated above, this was due to the change of path of the wave of contraction in the ventricle. (Tine in 2 secs.)

Lengthening of the above two forms of conduction has some place in the occurrence of ventricular extrasystoles. For if the normal impulse to the ventricle is delayed there is more opportunity for the formation of an ectopic focus . This is borne out by the fact that ventricular extrasystoles were always accompanied by marked delays in conduction.

(d) Contractility.

Lessened systole of the auricle and ventricle were constant accompaniments of the other alterations. During the third stage when heart block was manifest, lessening of systole was marked in every experiment. In the second stage it was not such a prominent feature, though it did occur to a smaller extent. In the more marked stages of heart block systole of the ventricle was very much curtailed and when the heart stopped after them, the lever remained in the diastolic position. Such lessening of systolic movement is due to impairment of contractility of the heart muscle.

Lastly, the alternation in the amplitudes of the ventricular beats which was noticed in the early stages of the action of bismuth, is due to depression of the contractility of the heart muscle.

(e) Tonicity.

Lessened tonicity would show itself in increased diastole of the auricle and ventricle. In the early stages of poisoning the opposite occurs and this/

this will be shown to be related to the fall in blood pressure. In the later stages of irregularity increased diastole was constantly observed and to such an extent that lessened tonicity must play an important part in its production. A fall in blood pressure, the result of failure of the heart, would give rise to an increased diastole, but in some experiments it was noted when the heart was recovering, that the recovery of the heart took place before that of the blood pressure. And, again, the lessened diastole was much in excess of that which could occur secondarily to the low blood pressure.

I conclude then, that lessening of tonicity of the heart muscle occurs to some extent.

Localisation of the action of bismuth on the heart.

It has been shown above that the inhibitory mechanism of the heart plays no part in the production of the alterations. It will be shown later that many of the changes occur in excised and perfused hearts. Thus one is led to the conclusion that the action of the soluble salts of bismuth is a local one on the heart muscle.

III. (Contd.).

(b) Action on the Blood Pressure.

The material for this section has been gleaned partly from the experiments where heart records were taken and partly from a number of experiments on cats where blood pressure tracings only were recorded.

The technique was the same as that described in the section on the effect of bismuth on the heart.

1. Effect of the intravenous injection of bismuth on the blood pressure.

A slight and temporary fall in pressure occurred after such small doses of bismuth as 0.5 mg. of the metal and was a constant accompaniment of any changes in the heart. Larger doses (1.5 mgs.) produced a more marked fall in pressure. Two phases of the fall could be made out, the first where a gradual and slight fall which was not accompanied by irregularity of the heart occurred, and a second phase where there was a marked fall with the reflection of cardiac irregularity in the blood pressure reading. The pressure recovered completely after small doses and after larger doses recovered to a certain extent but seemed to obey no law in the degree of recovery.

2. Discussion on the fall in blood pressure.

(a) First phase where the fall in pressure is slight.

The first question which must arise is whether this fall in pressure is secondary to the action of the/

the bismuth on the heart or whether a part of it is due to an action on the vascular mechanism. It has been observed before that a fall in blood pressure accompanied the slight changes in the heart after small doses and the connection between the two will be discussed here.

The changes in the heart which might have some relation to the fall in blood pressure are the lessening of the amplitudes of the auricle and ventricle, and these changes are seen to have a close connection with the fall in pressure. This is illustrated in the following graph:

Figure 34 /

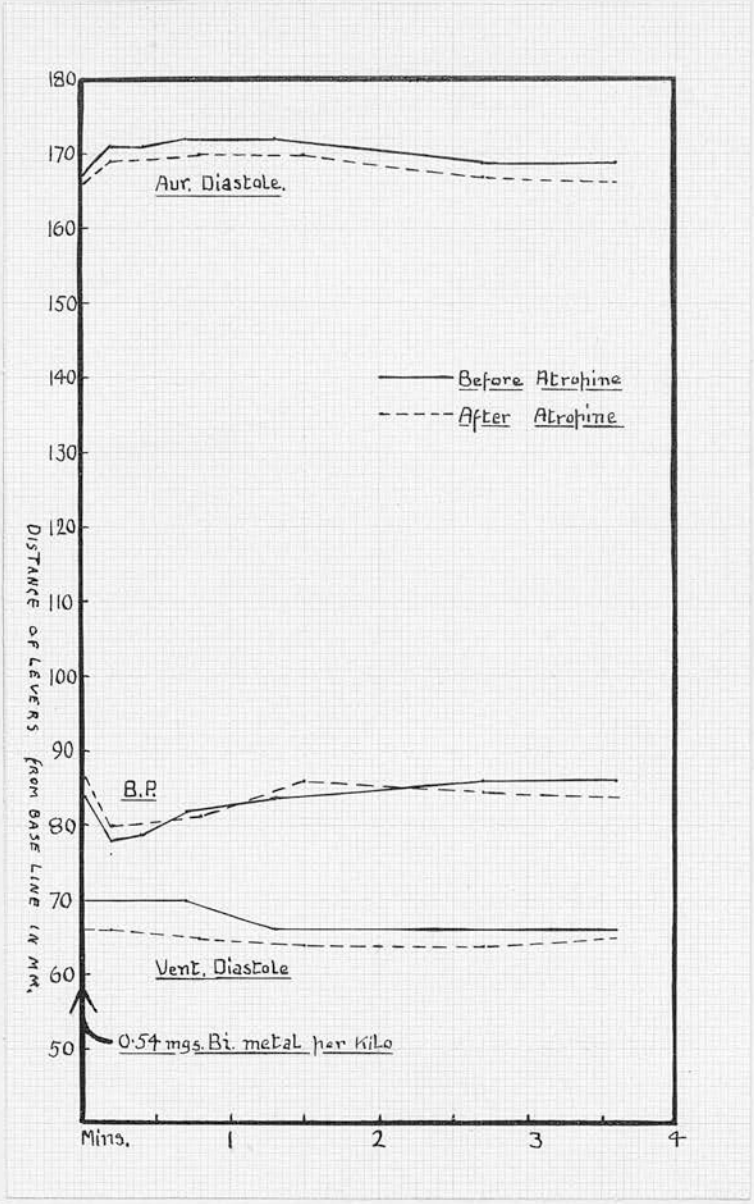


Figure 35.

Graph taken from Experiment No. 11 from a dog after 0.54 mgs. bismuth per kilo. Two injections were given, one before and one after atropine. It may be seen that the fall in blood pressure is accompanied by a lessening of diastole in the auricle and ventricle. The fall in blood pressure may be the cause or the result of the changes in amplitude. A lessening of diastole of the auricle would be expected if the fall in pressure were due to dilatation of peripheral vessels, because the blood content of the/

the chamber would be smaller. On the other hand, any fall of blood pressure due to heart impairment would be accompanied by an increased diastole.

It has been shown that, after bismuth, the tonicity of the heart muscle is diminished and this fact, in conjunction with the statement made above that any fall in blood pressure due to heart impairment would be accompanied by increased diastole makes it unlikely that the lessened diastole after bismuth is due to cardiac impairment. These facts suggest, rather, that there is a primary action on the vascular mechanism.

Experiments designed to determine how much of the fall in pressure is due to the action of bismuth on the vascular mechanism and how much on the heart, failed, because it was impossible to eliminate the occurrence of changes in the heart. Experiments on cats where bismuth was given before and after division of the splanchnic nerves were found to yield no results.

Again, several experiments were carried out where the volume of the intestine was recorded, but this only can be said, that the fall in pressure after small doses of bismuth is accompanied by a slight rise in intestinal volume and the fall in pressure where there is irregularity of the heart is accompanied by a slight fall in intestinal volume.

These /

These experiments were controlled by either giving amyl nitrite or producing artificial suffocation and noting the changes, towards the end of the experiments.

(b) Second phase where fall is marked.

The irregularities in the heart beat are usually reflected in the blood pressure tracings and the onset of these irregularities is always accompanied by a rapid fall in blood pressure. The following tracing shows these changes:

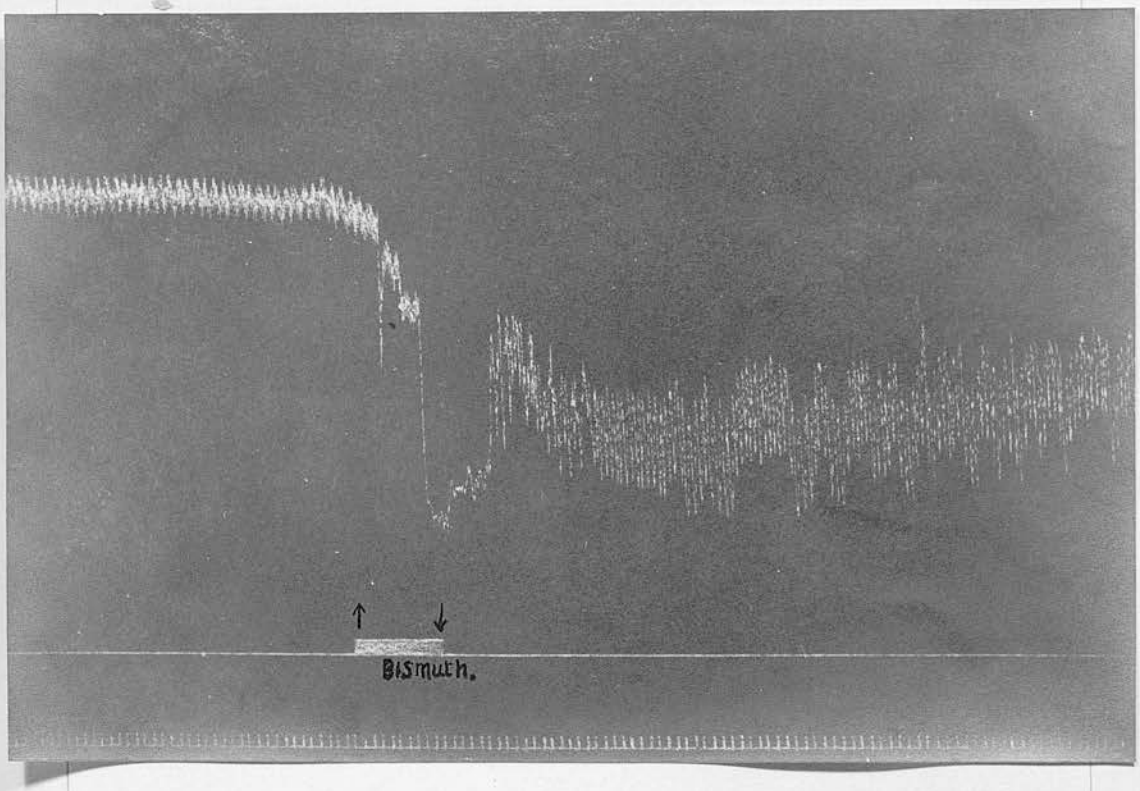


Figure 36.

Blood pressure tracing from the carotid artery of a cat. Between the arrows a dose of 1.78 mgs. bismuth metal per kilo. was injected. There can be

seen/

seen a preliminary gradual fall in pressure without marked irregularity in the heart. Then the heart beats weakly for a few seconds and the blood pressure is very low. The latter part of the tracing shows marked cardiac irregularity reflected in the blood pressure, which is low because of this heart failure. (Time in 2 sec. intervals).

3. The effect on the blood pressure varies with the time taken over the injection of the dose.

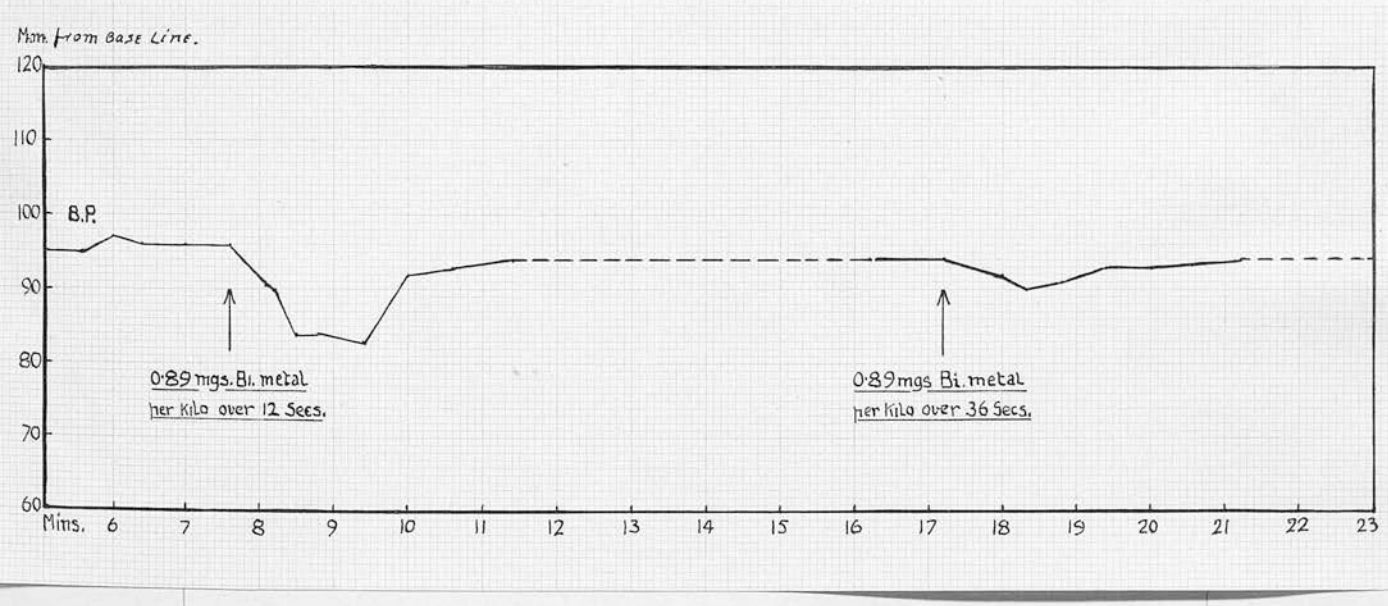


Figure 37 - shows that a second dose of bismuth similar in size to the first but injected more slowly gives a less marked fall in pressure. The graph is from an experiment on a cat where a blood pressure record was taken from the carotid artery.

The/

The fact that the time taken over the injection has a distinct relation to the effect produced is of importance in the question of the relation between dose and effect. This factor was eliminated in the experiments on the heart by giving the injections over the same period of time throughout.

4. Subsequent doses have a more marked effect on the blood pressure than the first.

This is shown in Figure 38:

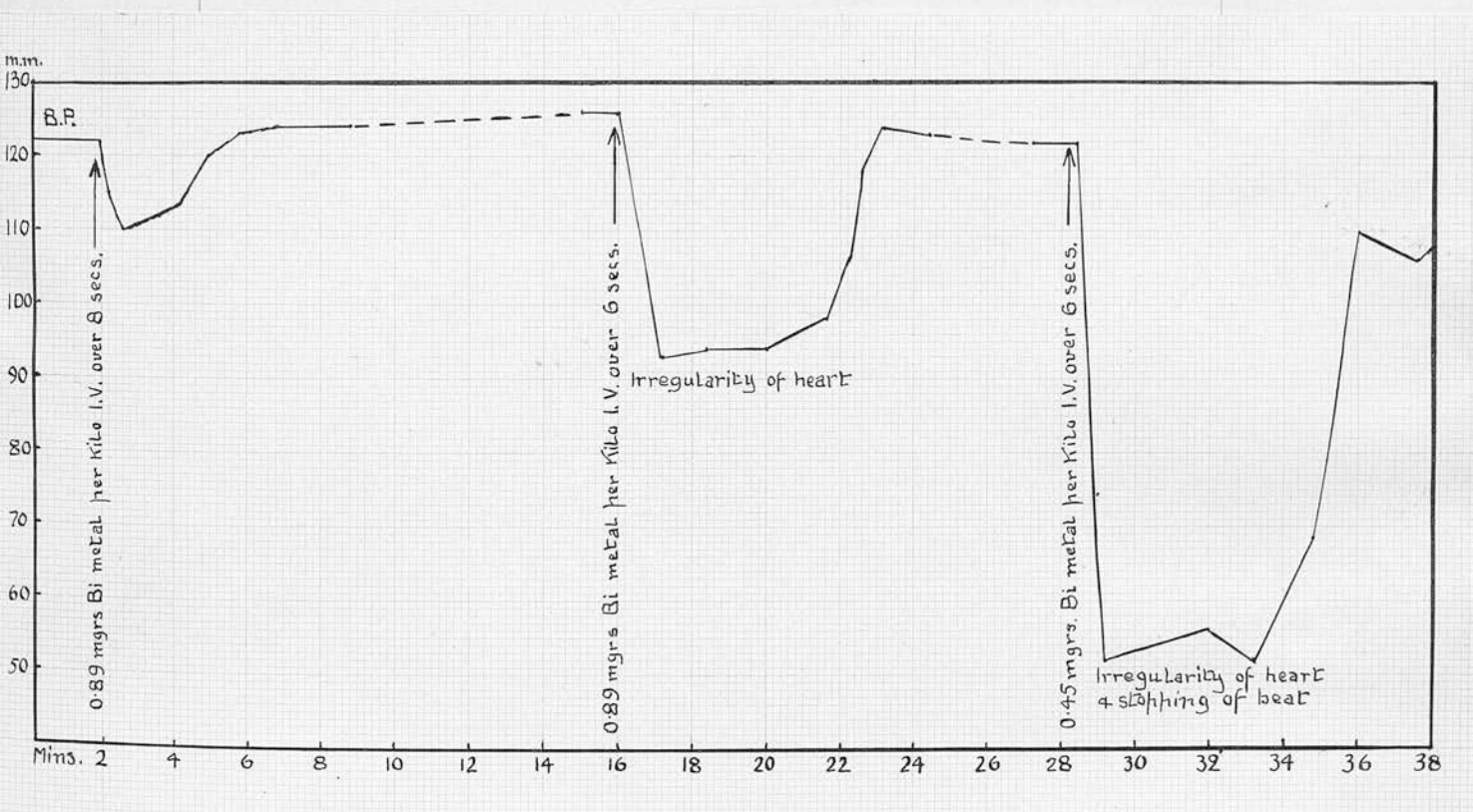


Figure 38. _ Here the third dose, which is half the size of the previous ones, gives a very much more marked and prolonged fall in pressure with stopping of/

of the heart. The graph is from an experiment on a cat where a blood pressure tracing was taken from the carotid artery. The injections were spread over the same period of time as far as possible.

Summary of the action of bismuth on the blood pressure

Intravenous injections of bismuth produce a fall in blood pressure, a fall divided into two phases: one, where the fall is slight and there is no cardiac irregularity reflected in the blood pressure tracing, and a second phase, where the fall is marked and cardiac irregularity is clearly evident in the tracing.

After large doses of bismuth, it is clear that most of the fall in pressure is due to the cardiac irregularity, but after small doses there is evidence of an additional elusive action on the vascular mechanism.

It was shown that the extent of the fall is relative to the size of the dose and the rapidity of the injection, and that second and subsequent doses produce a more marked effect than the first.

III (Contd.)

(c) Action on the Perfused Heart.

Preparation used and technique.

An apparatus was used consisting of two reservoirs for the perfusion fluids, and a tube heated to a constant temperature through which the fluids passed to the suspended heart. The pressure of fluid was, within narrow limits, constant throughout the series and the temperature was regulated to suit each heart and kept constant during the experiment.

The output of fluid from the heart was recorded by an automatic tipper (Condon) and marked by a signal on the tracing.

The same bismuth sodium tartrate was used as in the previous experiments, the solution being freshly made up each day.

Fresh Ringer's solution of the following formula was used:-

Sodium chloride	-	0.9 grams
Potassium chloride	-	0.4
Calcium chloride	-	0.2
Sodium bicarbonate	-	0.2
Distilled water	-	to 100 c.c.

Excised rabbits' hearts were used in all the experiments.

Below are given the results of nine typical experiments:-

Experiment No. 1/

Experiment No. 1.

Bismuth sodium tartrate 1 in 100,000 Ringer's solution.

Time	Alterations noted.
7m.12s.	Bismuth turned on
7m.22s.	Rate unaltered. Slight lessening of systole of ventricle. Auricle unaltered. Amplitude 3 mm.
7m.32s.	Rate unaltered. Systole of ventricle slightly lessened. Auricular amplitude lessened.
7m.52s.	Rate slowed by 3 beats per 10 secs. Systole of ventricle slightly lessened. Auricle scarcely moves lever.
8m.12s.	Same
9m.12s.	Same
10m.16s.	Bismuth turned off
15 mins.	Same. No recovery.

Experiment No. 2.

Bismuth sodium tartrate 1 in 50,000 Ringer's solution.

Time	Alterations noted.
4m.24s.	Bismuth turned on.
4m.32s.	No alteration in rate. Amplitude of auricle smaller. 20% decrease in systolic amplitude of ventricle.
4m.40s.	Slight slowing. Amplitude of auricle smaller. 50% decrease in systole of ventricle.
5m.24s.	Bismuth turned off. Heart same.
6m.24s.	Slight increase in systole of auricle and ventricle. Recovery of normal rate.
8m.24s.	Same
9m.24s.	Same.
14m.8s.	Bismuth turned on.
14m.50s.	Slight lessening of amplitude of ventricle. Auricle scarcely moves lever. Rate unaltered.
15m.40s./	

Experiment No. 2 (Contd.)

Time.	Alterations noted.
15m.40s.	Lessening of amplitude of ventricle. Auricle same. Rate slightly slower.
16m.10s.	Bismuth turned off.
18m.4s.	Auricle and ventricle recover amplitude. Rate remains same.

Experiment No. 3.

Bismuth sodium tartrate 1 in 10,000 in Ringer's solution.

Time	Alterations noted.
4m.8s.	Bismuth turned on.
4m.12s.	Auricular amplitude smaller. Ventricular systole smaller. Rate same.
4m.20s.	Auricle stopped beating. Rate slowed. Ventricular systole smaller. Output of fluid less.
5 mins.	Same.
6 mins.	Amplitudes the same. Rate slowed.
6m.14s.	Bismuth turned off.
6m.30s.	Same
7 mins.	Same.
8 mins.	Same. No recovery.

Experiment No. 4 /

Experiment No. 4.

Bismuth sodium tartrate 1 in 10,000 in Ringer's solution.

(Drum was going too fast for rate to be counted)

Time	Alterations in heart.
8m.42s.	Bismuth turned on.
8m.52s.	Lessening of systole of auricle. Slight lessening of systole of ventricle.
9m.32s.	Auricle stopped in diastole. Ventricular systole much smaller. Output of fluid from heart less.
9m.52s.	Auricle same. Ventricular amplitude still smaller. 50% of normal.
10m.32s.	Ventricular amplitude smaller. Output of fluid from heart less.
11m.22s.	Bismuth turned off.
11m.32s.	Auricular and ventricular amplitudes very small.
12 mins.	Ventricle beating slowly and weakly.
13 mins.	Slight recovery.
14 mins.	Recovery of both auricle and ventricle to about 50% of original.
16 mins.	Same.

Experiment No. 5/

Experiment No. 5.

Bismuth sodium tartrate 1 in 10,000 in Ringer's solution.

Time	Alterations in heart.
3m.2s.	Bismuth turned on.
3m.32s.	No alterations. Rate 17 per 10 seconds.
4 mins.	Auricular amplitude lessened. Systole of ventricle less. Rate 16 per 10 seconds. Output of fluid less.
4m.30s.	Rate 14 per 10 seconds. Amplitudes of auricle and ventricle less.
6 mins.	Rate 7 per 10 seconds. Auricle is beating too weakly to move lever. Ventricular systole smaller and diastole more pronounced. There is seen on observation of the heart 2-1 block.
6m.20s.	Ventricle 4 per 10 seconds. Systole of ventricle smaller and diastole more marked. 3-1 auriculo-ventricular block.
6m.40s.	Ventricle 3 per 10 seconds. 5-1 block. Amplitude smaller.
7m.10s.	Ventricle 1 per 10 seconds. There is 5-1 block. Ventricle is relaxed in diastole. Systole curtailed Output of fluid very much curtailed.
8m.2s.	Bismuth off.
9m.30s.	Same.
10m.10s.	Auricle starts moving lever. There is no block. Ventricular beats are stronger. Relaxation less pronounced and systole stronger.
11 mins.	Recovery to about 50% of original. Rate is 14 per 10 seconds. Output of fluid improved.
13 mins.	Same.

Experiment No. 6 /

Experiment No. 6.

Bismuth sodium tartrate 1 in 10,000 in Ringer's solution.

Time	Alterations in heart.
4m.40s.	Bismuth turned on.
4m.52s.	Slight lessening of systole of ventricle.
5m.30s.	Auricular amplitude very much smaller. Ventricular systole smaller and diastole more pronounced. Rate has quickened from 20 per 10 secs. to 28 per 10 secs.
6 mins.	Auricular amplitude very small. Ventricular systole smaller. Rate same. Output of fluid from heart less.
6m.4s.	Bismuth off.
7 mins.	Rate slower. Amplitude of ventricle slightly greater. Auricle same.
9 mins.	Rate 24 per 10 secs. Ventricle recovered slightly Auricle the same.
12 mins. to 18 mins.	The above experiment was repeated on the same heart. Quickening and changes in amplitude were given in the same way.

Experiment No. 7 /

Experiment No. 7.

Bismuth sodium tartrate 1 in 5000 in Ringer's solution,

Time	Alterations in heart.
4m.48s.	Bismuth turned on.
5m.30s.	Slowing of auricle and ventricle and slight alternation of amplitude of both chambers.
7m.30s.	Lessening of systolic movement of auricle and ventricle and more marked alternation of amplitude. Output of fluid lessened. Heart rate slowed by 30%.
8m.30s.	Same.
9m.30s.	Systole of auricle and ventricle less. Diastole increased. Rate slower. Alternation less marked. Output of fluid very small.
10m.30s.	Slower. Rate is diminished by 50%.
10m.44s.	Auricle and ventricle stop in diastole for 22 secs. Then there are 3 slow beats at intervals of 2 secs. and then another 20 secs. before there is another and weaker beat. This continues for 1 minute, the beats becoming very weak until the heart stops.
11m.50s.	Bismuth turned off.
13 mins.	No recovery.

Experiment No. 8 /

Experiment No. 8.

Bismuth sodium tartrate 1 in 5000 in Ringer's solution.

Time	Alterations in heart.
3m.32s.	Bismuth turned on.
4 mins.	Lessening of systolic amplitude of auricle and ventricle. Slight slowing of rate of heart.
4m.30s.	Auricular amplitude lessened. Ventricular systole much diminished and relaxation increased. Slowing of rate. Output of fluid from heart lessened.
5 mins.	Amplitude of auricle very small. More marked changes in amplitude of ventricle. Ventricle and auricle beat in sets of 3, the rate being much diminished.
5m.30s.	Same. Bismuth turned off.
6 mins.	Auricle not moving lever. Ventricle beating slowly, at one beat per 12 secs. Relaxation marked and systole furthered lowered. Output of fluid very small.
6m.30s.	Ventricle moves towards systole and rhythm recovers. Auricle recovers also. In 10 secs. amplitude and rate have increased to 20% below the normal. Output of fluid from heart still somewhat diminished.
9 mins.	No further recovery.

Experiment No. 9.

Bismuth sodium tartrate 1 in 1000 in Ringer's solution.

The infusion is kept on for 24 secs.

There is immediate lessening of amplitude of the ventricle, systole being the movement more curtailed. Similar changes are noted in the auricle, but to a less marked degree. There is slight slowing. In one minute the ventricle has stopped in diastole and the auricle is very weak. This lasts 10 secs. and then both chambers move towards systole and recover but the ventricular beats show alternation in amplitude. Amplitude is less than formerly and rate is slower. The recovery is almost complete in 110 secs. The output of fluid from the heart was diminished while bismuth was present in the perfusing fluid.

Summary of Experiments on Perfused Hearts.

The results do not allow of any attempt being made to classify them from the viewpoint of the concentration of bismuth salt in the perfusing fluid or the duration of the perfusion, for these factors have a varied bearing on the findings. It can be said, however, that to some extent the higher the concentration of bismuth, the more marked are the alterations and the more quickly do they come on.

Concentrations of 1:100,000 and 1:50,000 of the salt give slight alterations in 1-3 minutes.

Concentrations of 1:10,000 give a lessened amplitude of the auricle and ventricle, increased diastole of the ventricle, slowing, and stopping of the heart in diastole in from 30 seconds to 3 minutes. Lessening of the output of fluid from the heart accompanied these changes.

Auriculo-ventricular heart block was noted in one experiment (No. 5) and recovered when the bismuth was turned off.

Concentrations of 1:5000 and 1:2000 gave similar changes to those described above, the changes taking place in a shorter time and to a more marked degree.

The heart recovered in most experiments when the bismuth was turned off, though the recovery was but slight in some.

Below/

Below is given a tracing from Experiment No.8, showing the typical changes.

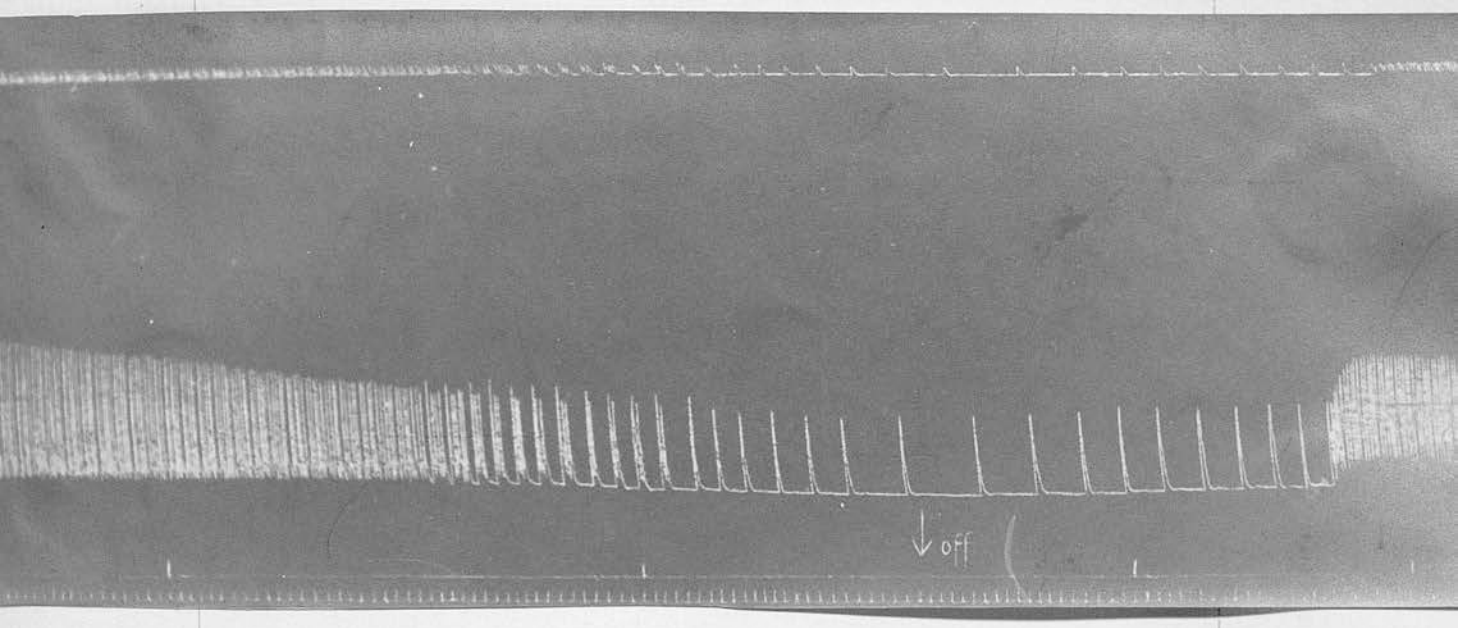


Figure 39.

Tracings from the auricle(upper) and ventricle (lower) from a rabbit's heart perfused with 1 in 5,000 bismuth sodium tartrate in Ringer's solution. The ventricle shows slowing of the rate, lessened systole and increased diastole. The line above the time record gives the rate of output of fluid from the heart. This rate of output of fluid is slowed while bismuth is being perfused. (Time in 2 secs.)

III (Contd.)

(d) Comparison of the effects of bismuth with the effects produced by some other metals.

This study was undertaken with a view to ascertaining whether any of the other heavy metals produced an action on the heart and blood pressure similar to that of bismuth.

The preparation of the animals for the experiments and the technique of the injections were the same as in the heart experiments with bismuth. Double salts of the metals were used and the doses have been calculated in terms of milligrams of metal per kilogramme of weight.

The actions on the circulatory system of the following metals were investigated:-

(1) Antimony (2 experiments recorded)
(2) Zinc
(3) Nickel
(4) Iron
(5) Tin
(6) Manganese
(7) Chromium
(8) Mercury
(9) Copper

Some details of the experiments are given below.

Experiment No. 24 /

Experiment No. 24. Cat, weight 4025 grams. Routine heart preparation. Antimony sodium tartrate given intravenously.

Time	Dose of antimony salt in mgs. of metal per kilo	Alterations in blood pressure	Alterations in Heart rate.
8 mins.	1 mg. over 6 secs.	No change	No change in amplitude
10m.20s.	1.5 mgs. over 10 secs.	Slow fall from 136 to 128 mm. B.P. recovers in 2 mins.	No changes
24m.8s.	3 mgs. over 6 secs.	Fall from 134 to 122 mm. Recovers in 2 mins. to 128 mm.	Auricular amplitude not changed Ventricular amplitude lessened by 2 mm. in both systole and diastole. Rate is slowed by 3 beats in 10 secs.
27 mins.		126 mm.	Amplitude of Auricle and ventricle as before injection. Rate still slowed.
29 mins.		124 mm.	Same
30 mins.	6 mgs. over 8 secs.	Gradual fall from 124 to 62 mm. in 12 mins.	Amplitudes of auricle and ventricle lessened to 30% of strength before injection. Lessening more marked in systolic phase. Rate of heart slowed by 8 beats in 10 secs.
34 mins.		76 mm.	There is an alternation of the beat of the ventricle. Every 2nd beat is weak. Beats are longer in duration.
38 mins.		66 mm.	Amplitude of auricle and ventricle same. Alternation still present. Slowing still present.
42 mins.		58 mm.	Same.
46 mins.		56 mm.	Same.
48 mins.	10 mgs. over 8 secs.	B.P. falls to 20 mm. in 3 mins.	Amplitude of auricle and ventricle less marked. Systole curtailed more. Rate slowed by another 6 beats in 10 secs.
52 mins.		16 mm.	Amplitudes of auricle and ventricle halved from those before 48 mins. Marked alternation of ventricular beats. Beats of long duration. A-V interval 20% longer than normal.
60 mins./			

Experiment No. 24 (Contd.)

Time	Dose of antimony salt inmgs. of metal per kilo.	Alterations in blood pressure	Alterations in heart rate.
60 mins.		10 mm.	Amplitudes very small. Marked alternans of ventricle. Rate diminished 40% of normal. Ventricle undergoes coarse fibrillation. Aur. beats for 1 min. very slowly, 10 per 10 secs. then stops in diastole.

Experiment No. 25. Cat, weight 3500 grams.
Routine heart preparation. Antimony sodium tartrate intravenously by a burette. Solution contained 14.8 mgs. antimony metal per 1 c.c.

Time	Dose of metal in mgs. per kilo.	Blood pressure in mm.	Rate of heart per 10 secs.	Alterations in heart.
1 min.	Infusion started			
5 mins.	on	154	35	Ventricular systole slightly lessened.
9 mins.		154	35	Same
12 mins.	29.6 mgs. given	142	35	Systole and diastole of auricle lessened. Systole of ventricle lessened.
15 mins.	on	134	33	Same
18 mins.		132	33	Same
20 mins.	44.4 mgs given	120	32	Diastole of ventricle lessened.
23 mins.	on	110	31	Auricular and ventricular diastole lessened. Ventricular systole increased.
28 mins	on	98	30	Same
31 mins.	on	96	28	Same
34 mins.	59.2 mgs. given	76	29	Systole and diastole of ventricle still further lessened.
37 mins.	on	58	27	Same.
40 mins.	on	50	26	Increased systole of ventricle. Lessenedamplitude of auricle and ventricle. Slight alternation of ventricle.
46 mins.				

Experiment No. 25 (Contd.).

Time	Dose of metal in mgs.per kilo.	Blood pressure in mm.	Rate of heart per 10 secs.	Alterations in heart.
46 mins.	on	38	19	More marked lessening of amplitude. Alternation more pronounced. A-V interval and duration of beat lengthened. Increased diastole of ventricle.
50 mins.	on	22	16	
53 mins.	on	22	16	Same.
55 mins.	118.4 mgs given	20	16	More marked diastole of ventricle and lessened systole. Alternation of ventricular amplitude.
58 mins.	on	22	16	Amplitude of auricle very small. Beats of weaker strength.
62 mins.	126.8 mgs given	12	12	A-V interval prolonged. Duration of beats prolonged.
65 mins.	Infusion stopped	10	12	Same
68 mins.	off	10	12	Beats weaker. Alternation pronounced.
71 mins,	off	8	10	Beats weaker. Diastole more marked.
72 mins.	off	base line	--	Both auricle and ventricle stopped in diastole suddenly. Animal has a convulsion and dies.

Experiment No. 26. Cat, weight 3600 grams.
Zinc ammonium sulphate given intravenously.

Time	Dose of metal in mgs. per kilo.	Alterations in blood pressure.	Alterations in heart.
3 mins.	0.28 mgs. over 4 secs.	No alterations	No alterations.
6 mins.		152 mm.	
8 mins.	0.56 mgs. over 6 secs.	Abrupt fall in B.P. to 136. Recovers to 150 in 20 secs.	No alterations in auricle. Ventricular systole increased and diastole lessened. Increase in amplitude of ventricle. Rate not altered.
16 mins.		136 mm.	Recovery of normal amplitude.
19 mins.		134 mm.	Same
25 mins.		Same	Same
29m.4s.	2.26 mgs. over 8 secs.	Lowering of B.P. to 100 recovering partly in 3 mins.	Rate of heart slowed by 3 beats per 10 secs. Diastole of ventricle unaltered. Increase in systolic movement of ventricle. Auricle unchanged.
32 mins.		128 mm.	Amplitude of ventricle less than before injection.
35 mins.		128 mm.	Same
40 mins.		126 mm.	Same
43m.4s.	3.4 mgs. over 10 secs.	Fall of B.P. to 96 Recovers to 120 in 4 mins.	Diastole of auricle and ventricle unchanged. Systole more marked in both chambers. Rate unaltered.
46 mins.		116 mm.	Amplitude slightly less than before injection
55 mins.		118 mm.	Same.
59mins.	4.5 mgs. over 8 secs.	Gradual fall in B.P.	Rate unaltered. Amplitude of auricle and ventricle lessened more especially in systole. Slight alternation of ventricular amplitude.
62 mins.		68 mm.	Amplitude of auricle and ventricle lessened. Rate slowed by 4 beats per 10 secs.
66 mins.		54 mm.	Amplitudes lessened. Marked alternate beating of ventricle. Rate slower by 2 beats per 10 seconds.
72 mins.			

Experiment No. 26 (Contd.)

Time	Dose of metal in mgs. per kilo	Alterations in blood pressure in mm.	Alterations in heart.
72 mins.		42	Heart slow. Amplitude very small. Alternation marked in the ventricle.
74 mins.		24	Amplitude very small. Rate lessened 30 per cent. of normal. A-V interval lengthened.
78 mins.		Base line	Auricle and ventricle stop simultaneously after a few small and weak beats. They stop in diastole. Animal has some convulsions before death.

Experiment No. 27. Cat, weight 3450 grams.
Routine heart preparation. Nickel ammonium sulphate given intravenously.

Time	Dose of metal in mgs. per kilo.	Blood pressure in mm.	Alterations in heart.
16 mins.	0.6 mgs. over 4 secs.	Lowered in 20 secs. from 102 to 92 Recovers to 100 in 1 min.	Amplitude of auricle and ventricle not altered. Rate of heart slowed by 2 beats per 10 secs.
22 mins.	1.2 mgs. over 8 secs.	Lowered in 24 secs. from 100 to 74. Does not recover	Lessened systole of both auricle and ventricle. Auricular diastole not altered. Ventricular diastole lessened by 3 mm. Rate slowed to 3 beats per 10 sec. less than normal.
26 mins.		62	Same
28 mins.		62	Systole of auricle and ventricle have recovered to a slight extent.
32 mins.	2.4 mgs. over 10 secs.	B.P. lowered in 1 min. to 46 mm.	Systole of auricle and ventricle lessened by 10 mm. Diastole lessened to a less extent. Rate of heart same as before injection.
35 mins.		46	Same
38 mins.		46	Same
43 mins.	4.8 mgs. over 10 secs.	B.P. lowered in 40 secs. to 26 mm.	Amplitude of auricle and ventricle becomes 50% less than before injection. Lessening of systole more marked than lessening of diastole. Rate slowed by 75% of the normal.
43m.30s.		26	Lessening of amplitude more marked.
44 mins./			

Experiment No. 27 (Contd.).

Time	Dose of metal in mgs. per kilo.	Blood pressure in mm.	Alterations in heart
44 mins.		26	Same
48 mins.		28	Amplitude of auricle and ventricle has recovered to a slight extent. Rate same.
52 mins.		26	Same
55 mins.		26	Recovery more marked. Duration of beat and A-V interval 50% increased.
56mins.	9.6 mgs. over 12 secs.		The heart stops in diastole after 30 secs. Both chambers stop simultaneously and the stoppage is preceded by great lessening of the amplitude of the auricle and ventricle so that they were but 10% to 15% of the normal.

Experiment No. 28 /

Experiment No. 28. Cat, weight 2800 grams.
Routine heart preparation. Iron potassium tartrate given intravenously.

Time	Dose of metal in mgs. per kilo.	Blood Pressure in mm.	Heart rate per 10 secs.	Alterations in heart
2 mins.		156	38	
3 mins.	0.7 mgs. over 6 secs.	Gradual fall in B.P. Recovery in 3 mins.	36	Slight lessening of diastolic movement of ventricle. Auricle unchanged.
8 mins	1.4 mgs. over 6 secs.	B.P. falls to 120 and recovers in 2 mins. to 144	36	Slight lessening of amplitude of auricle. Ventricle unchanged.
11 mins.		Recovered to 144	36	Recovered
15 mins.	2.8 mgs. over 10 secs.	There is a marked fall of B.P. in 6 secs. and recovering in 3 mins.	35	Systole of auricle and ventricle more complete. Diastole less. Amplitude lessened by 10%.
20 mins.		118	35	Recovered to a great extent.
27mins.	5.6 mgs. over 10 secs.	Fall of B.P. as after previous dose.	34	Changes in auricle and ventricle slightly more marked than after previous dose.
30 mins.		B.P. falling slowly	28	Gradual lessening of amplitudes of auricle and ventricle
35 mins.		46	24	Gradual lessening of amplitudes of both chambers of heart.
38 mins.		26	22	Same
40 mins.		12	18	Auricle has stopped in diastole. Ventricle still beats with small amplitude.
43 mins.		12	20	Auricle recovered and ventricle responds with a weak contraction to every 3rd impulse. Duration of beat is long and A-V interval lengthened
46 mins.		12	20	Same.
50 mins.		Base line	?	Auricle has stopped beating. Ventricle beats weakly and very slowly.
52 mins.		do.	-	Auricle and ventricle have stopped in diastole. Animal has a convulsion and dies.

Experiment No. 29. Cat, weight 3100 grams.
Routine heart preparation. Tin ammonium chloride given intravenously.

Time	Dose of metal in mgs. per kilo.	Blood pressure in mm.	Alterations in heart.
8 mins.	0.9 mgs. over 6 secs.	B.P. lowered from 60 to 52 mm. in 8 mins.	Systole and diastole of auricle and ventricle lessened to a small extent. Amplitude of ventricle lessened by 5 mm. Rate slowed from 32 to 29 per 10 secs.
10 mins.		52	Same.
16 mins.		52	Amplitudes of auricle and ventricle do not recover. Rate remains at the new rate.
16m.8s.	1.8 mgs. over 8 secs.	B.P. falls in 10 secs. to 48	Amplitude of auricle does not change. Systole and diastole of ventricle diminished slightly. Rate slowed to 27 per 10 secs.
18 mins.		46	Same
20 mins.		46	Same.
25 mins.	2.7 mgs. over 8 secs.	B.P. falls to 36 in 3 mins. and does not recover	Diastole of ventricle lessened. Systole remains same. Diastole and systole of auricle lessened about 5%. Rate 27 per 10 secs.
28 mins.		Same	Same. Rate 27 per 10 secs.
31 mins.		34	Same
36 mins.		36	Slight recovery of amplitude of auricle and ventricle.
38 mins.	3.6 mgs. over 12 secs.	B.P. falls to 14 in 12 secs.	Diastole of ventricle curtailed very much in first 12 secs. Systole lessened to smaller degree. Amplitude of auricle lessened 10% and rate slowed to 23 per 10 secs.
38m.20s.		6	Auricle stopped in diastole. Ventricle continues to beat in slow rhythm, 21 per 10 secs. Ventricular amplitude lessened and lever displaced to diastole.
38m.36s.		6	Auricle stopped. Ventricular amplitude smaller and rate slowed to 16 per 10 secs.
39 mins.		Base line	Heart has stopped for 4 secs. in diastole
41m.6s. /			

Experiment No. 29 (Contd.).

TIME	Dose of metal in mgs. per kilo.	Blood pressure in mm.	Alterations in heart.
41m.6s.		4	Ventricle has small amplitude and beats at 6 per 10 secs. Auricle not moving.
42 mins.		4	Auricle has restarted beating and gives one beat for every two or three of ventricle. There is heart block with an A-V interval thrice the normal for 1 minute, then heart stops.
44m.30s.		Base line	Both chambers stopped in diastole.

Experiment No. 30. Cat, weight 3050 grams.
Routine anaesthesia and heart preparation.
Manganese lacto-phosphate given intravenously.

Time	Dose of metal in mgs. per kilo.	Blood pressure in mm.	Alterations in heart
3 mins.	0.25 mgs. over 8 secs.	Abrupt fall in pressure from 122 to 82 mm. Slow recovery in 3 mins.	Shortening of systolic and diastolic auricular movements to a slight extent. Ventricular lever moves towards systole Diastole is lessened by 5 mm. and systole increased by 7 mm. Rate slowed by 2 beats per 10 secs.
12 mins.		120	Recovery of normal amplitude.
14 mins.	0.5 mgs. over 10 secs.	Abrupt fall in B.P. from 118 to 76 mm. After 1 min. there is gradual recovery of pressure until in 6 mins. it has reached 114 mm.	Amplitude of auricle same. Ventricle moves 7 mm. towards systole, and diastole is less by 4 mm. Rate is slower by 2 beats in 10 secs.
20 mins.		112	As before injection.
24 mins.		110	do.
26 mins.	1 mg. over 8 secs.	Fall in B.P. to 62 mm. Gradual but partial recovery in 7 mins. to 78 mm.	No change in auricle. Ventricle shows slightly more marked systole and smaller diastole. Rate is slowed by 3 beats in 10 secs.
28 mins.		64	Heart has recovered former amplitude.
33 mins.			

Experiment No. 30 (Contd.).

Time	Dose of metal in mgs. per kilo.	Blood pressure in mm.	Alterations in heart.
33 mins.		78	Heart has recovered former amplitude.
44mins.	2 mgs. over 12 secs.	Fall in B.P. from 76 to 34 mm. No recovery. Pressure remains at 34 mm.	Auricle shows slightly lessened amplitude in both diastole and systole. Ventricle shows a movement of 3 mm. towards systole. Slowing to extent of 5 beats in 10 secs.
47 mins.		34	Amplitudes of auricle and ventricle are smaller by 6-10 mm.
50 mins.		32	Amplitudes and rate the same.
56 mins.		30	Amplitudes smaller by 2 mm. and 4 mm. Rate same.
60mins.	6 mgs. over 8 secs.	18	Systole of auricle curtailed and diastole also to a less extent. Amplitude becomes progressively smaller. Systole of ventricle becomes less marked, and to a less extent there is lessening of diastole.
63 mins.		Base line	Rate becomes much slower until it is half of what it was. This becomes more pronounced and both chambers stop simultaneously in diastole.

Experiment No. 31 /

Experiment No. 31. Cat, weight 3260 grams. Routine heart preparation. Chromium sodium oxalate intravenously.

Time	Dose of metal in mgs. per kilo.	Blood Pressure in mm.	Alterations in heart
10m.30s.	1.8 mgs. per kilo over 10 secs.	No alteration	No alteration
12m.10s.	3.6 mgs. per kilo over 10 secs.	do.	do.
14m.20s.	3.5 mgs. per kilo over 4 secs.	Slight fall in B.P. recovering in 10 secs.	No alteration.
17 mins.	4.8 mgs. per kilo over 10 secs.	No alteration	do.
24 mins.	7.2 mgs. per kilo over 10 secs.	do.	do.
32 mins.	14.4 mgs. per kilo over 10 secs.	Slight and transient fall in blood pressure	Slight weakening of systole of auricle. No alteration in ventricle. Rate of heart unaltered.

Experiment stopped.

Experiment No. 34./

Experiment No. 34. Cat, weight 3200 grams. Routine heart preparation. Mercuric cyanide 1% given intravenously.

Time	Dose of metal in mgs. per kilo.	Blood Pressure in mm.	Alterations in heart.
1 min.	0.8 mgs. over 4 secs.	No alterations	No alterations
6 mins.	1.6 mgs. over 4 secs.	No alterations	do.
15 mins.	2.6 mgs. over 6 secs.	Gradual fall of B.P. from 114 to 84 mm. in 5 mins.	Lessened amplitude of the auricle. Ventricle lessened in diastole and increased in systole and amplitude is less. There is slowing by 4 beats per 10 secs. A-V interval slightly lengthened.
17 mins.		88	Auricle lessened in amplitude and irregular. Beats occur at irregular intervals. Ventricle shows lessened amplitude and beats in sets of 3. The first beat of this set is of long duration; next shorter; the next very short, and then a pause.
18m.30s.		86	Same. Rate unaltered.
22 mins.		92	Heart regular. Amplitude of both chambers is less and ventricle is displaced towards systole.
25 mins.		92	Same. Rate same.
30 mins.		90	Same.
36 mins.	4 mgs. over 6 secs.	Abrupt fall in B.P. to 60 mm. in 2 mins.	Amplitude of auricle becomes small and rhythm irregular in time and force. Amplitude of ventricle becomes small and it responds to auricle after a longer interval than before. Slowing by 4 beats per 10 secs.
36m.40s.		Base line	The auricle and ventricle stopped simultaneously in diastole. Heart is recovering a slow rhythm.
37 mins.			Some convulsions present.
38 mins.		24	Auricle beating irregularly at rate of 5 beats per 10 secs. slower than formerly. The ventricle responds only to every 3rd or 4th auricular stimulus. Amplitude of ventricle is small and diastole curtailed.
39m.10s.			

Experiment No. 34 (Contd.).

Time	Dose of metal in mgs. per kilo.	Blood pressure in mm.	Alterations in heart.
39m.10s.		22	3-1 and 4-1 auriculo-ventricular block.
40m.30s.		20	Same. Auricular amplitude very small.
42 mins.		18	Amplitude of ventricle smaller. Auricular rate half of normal.
44 mins.		12	Ventricle responds irregularly to every 3rd or 4th auricular stimulus. A-V interval is doubled.
47 mins.		10	Auricular and ventricular amplitudes small. 5-1 block present. Rate slower.
49 mins.		Base line	After a few abortive beats auricle and ventricle stop simultaneously in diastole. Animal has a few spasms and dies.

Experiment No. 35 /

Experiment No. 35. Cat, weight 3000 grams. Routine heart preparation. Copper ammonium sulphate given intravenously.

Time	Dose of copper in mgs. per kilo.	Blood Pressure in mm.	Heart rate per 10 secs.	Alterations in heart.
2 mins.		78	36	
3m.10s.	0.4 mgs. metal over 4 secs.	No alteration	36	No change in ventricle. Slight lessening of amplitude of auricle.
4 mins.			36	Heart recovered.
7m.30s.	1.2 mgs. metal per kilo over 6 secs.	Slight fall in B.P. lasting 1 min.	37	Lessening of amplitudes of auricle and ventricle to a slight extent.
9 mins.		Recovered	37	Recovered
16 mins.	2.4 mgs. metal per kilo over 6 secs.	Gradual fall of B.P. to 64 mm.	38	Amplitudes of auricle and ventricle lessened, especially systole.
17m.10s.		62	37	Amplitudes of auricle and ventricle further reduced.
18m.30s.		46	35	Amplitude of auricle very small. Systolic movement of ventricle much curtailed. No irregularity in rhythm
19 mins.		26	?	Auricle stops in diastole for 3 mins. Ventricle beats with small amplitude and misses some beats every 3rd or 4th auricular beat.
22 mins.		Base line	?	Auricle stopped. Ventricle beats weakly and regularly but slowly.
23m.20s.		24	32	Auricle and ventricle recovering.
26 mins.		28	34	Both chambers recovered.
32 mins.		Same	34	Same.
34 mins.	4 mgs. metal per kilo over 8 secs.	Gradual fall of B.P, to 18	30	Marked lessening of systolic amplitude of auricle. Lessening to smaller extent of ventricular systole. Duration of beats and A-V interval longer.
37 mins.				

Experiment No. 35 (Contd.).

Time	Dose of copper in mgs. per kilo.	Blood Pressure in mm.	Heart rate per 10 secs.	Alterations in heart
37 mins.		12	18	Amplitudes very small.
42 mins.		Base line		Auricle has stopped in diastole. Ventricle beats weakly for about 2 minutes.
45 mins.		12	16	Auricle restarts to beat weakly. Ventricle beats more strongly. A-V interval and duration of beats double the normal in length.
48 mins.		16	22	Auricle and ventricle have recovered to a large extent.
55 mins.		12	24	Same.

Experiment ended.

Summary/

Summary of Experiments and Comparison with Experiments on Bismuth.

ANTIMONY.

(a) Minimum dose. 2.5 mgs. antimony metal per kilo was the lowest dose which produced changes in the heart and blood pressure.

(b) Effect on Heart.

1. Rate was slowed.
2. No measurable changes in conduction between auricle and ventricle.
   Slight increase in duration of the ventricular beat.
3. Lessened contractility of auricle and ventricle shown by weakness of beat and alternation of the ventricular amplitude.

Figure 40. /

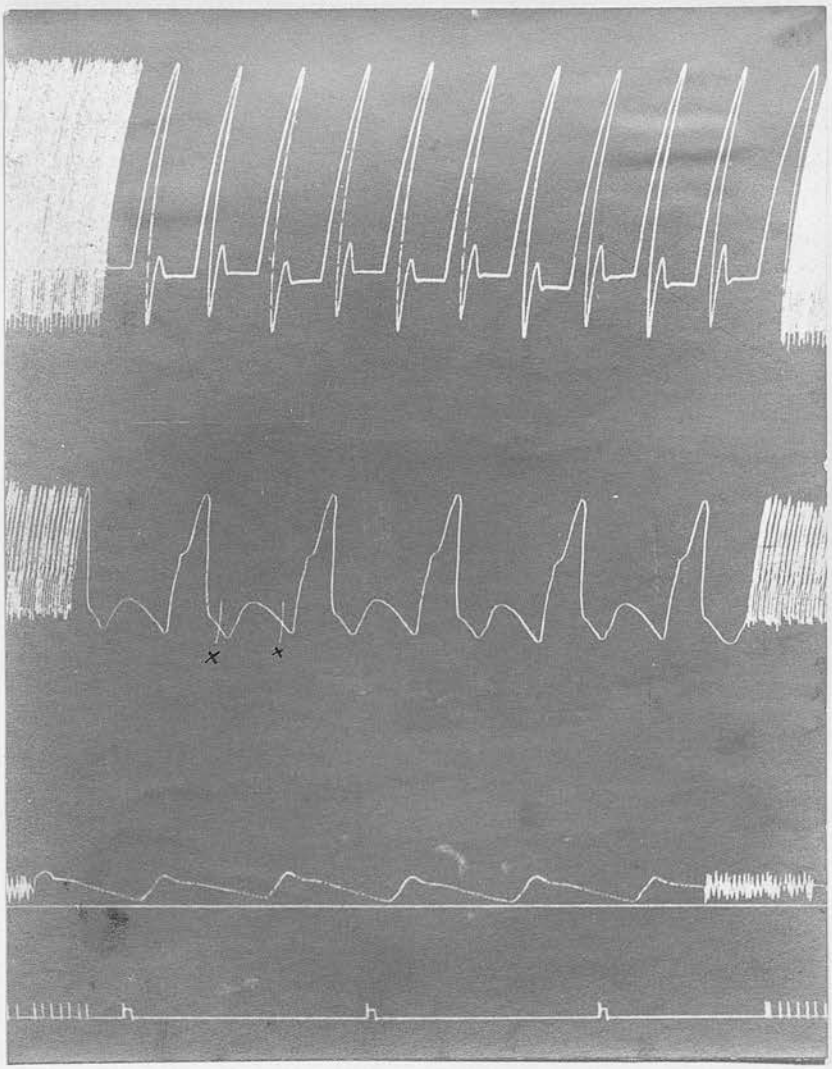


Figure 40.

Tracings from the auricle (upper) and ventricle (lower and a blood pressure tracing from a cat after 126.8 mgs. antimony metal per kilo intravenously. The amplitudes of both auricle and ventricle are very small and there is marked alternation in the ventricular beats. The A-V intervals are only slightly prolonged. This condition is different from that which would be produced by bismuth in that after bismuth, conduction would be markedly affected and heart block would be present. The alternation in the above tracing is not due to alterations in conduction but to weakening of contractility. The blood pressure is at the base line. (Time in 2 second intervals)

4. There was lessened tonicity of ventricle manifested by an increased diastole.

(c) Effect on Blood Pressure.

A fall in pressure occurred after small doses before changes in the heart came on. After larger doses there was a more marked fall accompanied by changes in the heart.

(d) Comparison with Bismuth.

The slowing, lessened contractility and lessened tonicity occur after bismuth, but to a much more marked extent. Antimony does not present the marked lengthening of conduction seen after bismuth. Bismuth is toxic in much smaller doses than antimony.

ZINC.

(a) Minimum Dose.

0.84 mgs. zinc metal per kilo gave changes in the blood pressure.

(b) Effect on Heart.

1. Rate was slowed.
2. No changes in conduction.
3. Lessened contracility of auricle and ventricle.
4. No observable changes on tonicity.

(c) Effect on Blood Pressure.

Small doses have a marked but transitory effect on the blood pressure without alteration in the amplitude of the heart.

(d) /

Iron (Contd.)

(b) Effect on Heart (Contd.).

3. Contractility lessened.
4. Tonicity of ventricle lessened.

(c) Effect on Blood Pressure.

There was a fall and recovery after small doses without changes in the heart. After larger doses the pressure fell as the heart became impaired.

(d) Comparison with Bismuth.

The slowing, lengthened conduction, lessened contractility and tonicity present similarities to the action of bismuth. The heart block with iron, however, only comes on in the later stages of poisoning when the heart is very weak.

TIN.

(a) Minimum dose.

0.9 mgs. tin metal per kilo lessened the amplitudes of the auricle and ventricle and lowered the blood pressure.

(b) Effect on Heart.

1. Rate was slowed.
2. There was an increase in A-V conduction and duration of the ventricular beat, to a slight extent in the early stages and to a more marked extent in the late stages where there was heart block before death.
3. Contractility lessened.
4. Tonicity lessened.

(c) Blood Pressure.

Blood pressure was lowered after small doses and fell as the contractility of heart was lessened.

(d) /

Zinc (Contd.)

(d) Comparison with Bismuth.

The slowing and lessened contractility present some slight similarity to the action of bismuth.

NICKEL.

(a) Minimum dose.

0.5 mgs. nickel metal per kilo gave lowering of blood pressure.

(b) Effect on Heart.

1. Rate was slowed markedly.
2. No measurable changes in conduction.
3. Lessened contractility of auricle and ventricle.
4. Tonicity unaltered.

(c) Effect on Blood Pressure.

Small doses gave a temporary abrupt fall in blood pressure without changes in the heart.

(d) Comparison with Bismuth.

The slowing and lessened contractility represent some slight similarity to the action of bismuth.

IRON.

(a) Minimum dose.

0.7 mgs. iron metal per kilo gave a slight fall in blood pressure.

(b) Effect on Heart.

1. Rate was slowed.
2. In the late stages of poisoning there was a lengthened A-V interval and alengthened duration of the ventricular beat. This brought on heart block.

3. /

TIN (Contd.),

(d) Comparison with bismuth.

The lengthened conduction and lessened contractility and tonicity bear some resemblance to the action of bismuth. Heart block only takes place in the late stages of poisoning with tin.

MANGANESE.

(a) Minimum dose.

0.25 mgs. metal per kilo gave lessening of amplitudes of auricle and ventricle and a fall in blood pressure.

(b) Effect on Heart.

1. Rate slowed.
2. No measurable change in conduction.
3. Lessened contractility of auricle and ventricle.
4. Tonicity unaltered.

(c) Effect on Blood Pressure.

This was abruptly lowered after small doses before the alterations in the heart became marked.

(d) Comparison with bismuth.

The slowing and lessened contractility present slight similarity to the action of bismuth.

CHROMIUM /

CHROMIUM.

(a) Minimum dose.

3.5 mgs. metal per kilo gave a fall in blood pressure.

(b) Effect on Heart.

1. Rate showed no alteration.
2. No alteration in conduction.
3. Contractility slightly lessened.
4. Tonicity unaltered.

(c) Blood Pressure.

Fails slightly before changes in the heart occurred.

(d) Comparison with bismuth. Is but slight.

MERCURY.

(a) Minimum dose.

5 mgs. in repeated doses gave changes in amplitudes of auricle and ventricle.

(b) Effect on Heart.

1. Rate was slowed.
2. A-V conduction and duration of beat were lengthened. Heart block of various types resulted.
3. Contractility of auricle and ventricle lessened.
4. Tonicity unaltered.

(c) Effect on Blood Pressure.

This fell as the heart was affected.

(d) /

MERCURY (Contd.)

(d) Comparison with Bismuth.

Mercury offers a close similarity in the manner in which the conduction is increased and heart block comes on and in the lessened contractility of the auricle and ventricle.

COPPER.

(a) Minimum dose.

0.4 mgs. metal gave slight changes in the heart.

(b) Effect on Heart.

1. Rate was at first slightly quickened. Then slowed.
2. There was lengthening of A-V interval and duration of ventricular beats. No heart block observed.
3. Contractility lessened.
4. Tonicity lessened.

(c) Effect on blood pressure.

There was a fall in blood pressure which followed on the changes in the heart rate and amplitude.

(d) Comparison with bismuth.

The slowing, the lengthening of conduction, and the lessening of contractility and tonicity present some similarity to the action of bismuth.

IV. THERAPEUTIC EFFECT IN EXPERIMENTAL SYPHILIS.

This investigation was carried out with the object of relating the curative to the tolerated and toxic doses.

Historical.

Sazerac and Levaditi in 1921[29] were the first to show that bismuth had a definite curative action in experimental syphilis. Numerous investigators have since investigated its effect in various forms of experimental syphilis and in human syphilis, and the results noted by Sazerac and Levaditi have been fully supported. In the above and in some later papers[10, 12, 30, 31], Sazerac and Levaditi give their results with various salts of the metal in rabbits infected with the virus dermatrope and the virus neurotrope from human syphilis and spontaneous spirochaetosis of rabbits - spirochaeta cuniculi. They say that 10 mgs. bismuth metal per kilo intramuscularly, and 0.015 grams of citrate of bismuth and ammonia per kilo intramuscularly rid rabbits of the infection in about four days. Similar results were obtained with a bismuth tartrate. In guinea-pigs infected with trypanosomiasis - virus nagana - they found that 0.2 grams per kilo and 0.06 grams per kilo of the tartrate of bismuth potassium

and/

and sodium subcutaneously resulted in the disappearance of the infection in 48 hours, that 0.1 gram gave similar results in 24 to 48 hours but that relapse occurred in 12 to 15 days.

Five years before the above work was published, Sauton and Robert in 1916[32] had found that the tartrate of bismuth and sodium gave good results in spirillosis of hens and trypanosomiasis in guinea-pigs. Recovery was obtained in spirillosis of hens by the intravenous injection of 10 mgs. of the metal in two doses.

Giemsa[11] used the tartrate of bismuth potassium and sodium intravenously in rabbits and found that 0.7 mgs. per kilo of the metal cured the infection. He estimated the curative-tolerated coefficient as 1 to 6 or 7.

Pomaret and Didry[14] say that the C/T coefficient in dogs after intramuscular injection of bismuth tartrate solution is 1/8.5.

Levaditi[33] states that very small quantities of bismuth metal are sufficient to rid rabbits of infection, spirochaetes disappearing after a dose of 0.317 mgs. per kilo.

Levaditi, Nicolau, Salgue and Schoen[34] came to the conclusion that bismuth can kill spirochaetes in rabbits when present in the body in quantities impossible to detect chemically.

The following experiments were carried out on rabbits whose genitalia had been inoculated with spirochaeta/

spirochaeta cuniculi. Supplies of the spirochaete were kindly made available for me by Professor Mackie of the Bacteriology Department of the University of Edinburgh.

When the lesions in the rabbits had become fully developed determinations were made, by means of a microscope fitted with dark ground illumination apparatus, of the presence of spirochaetes in the lesions and of the approximate number of spirochaetes in a field. After the injection of bismuth this proceeding was carried out at intervals until the spirochaetes disappeared, several counts being made each time. The healing of the lesions was not taken as a guide of recovery chiefly because they varied in size and therefore their ability to heal differed.

Experiment No. 1. Rabbit, weight 1495 grams.

Lesion on genitalia the size of two match-heads. Spirochaetes plentiful.

1st day.

12 noon. 0.44 mgs. bismuth metal intravenously per kilo.

2nd day.

10 a.m. Spirochaetes present but few in number.

4 p.m. No spirochaetes found.

10th day. Lesion healed.

Experiment No. 2 /

Experiment No. 2. Rabbit, weight 2070 grams.

Lesion on genitalia rather smaller than in 1st rabbit. Spirochaetes plentiful.

1st day.
12 noon. 0.88 mgs. bismuth metal intravenously per kilo.

2nd day.
10.30 a.m. No spirochaetes present.

10th day. Lesion very much smaller.

Experiment No. 3. Rabbit, weight 1275 grams.

Large lesion on genitalia. Spirochaetes plentiful.

1st day.
12 noon. 1.76 mgs. bismuth metal intravenously per kilo.

2nd day.
12 noon. No spirochaetes present.

10th day. Lesion smaller.

Experiment No. 4. Rabbit, weight 1530 grams.

Medium sized lesion genitalia. Spirochaetes abundant.

1st day
12 noon. 3.5 mgs. bismuth metal intravenously per kilo.

2nd day
2 p.m. No spirochaetes found.

10th day. Lesion almost healed.

Experiment No. 5. /

Experiment No. 5. Rabbit, weight 1105 grams.

Large lesion on genitalia. Spirochaetes abundant.

1st day
12 noon. 4.45 mgs. bismuth metal intravenously per kilo.

2nd day.
2.30 p.m. No spirochaetes found.

10th day. Lesion smaller.

Experiments Nos. 6 and 7. - Controls. No injections given.

Summary of Experiments on curative effect of bismuth.

Few in number though these experiments be, they are sufficient for their purpose in that they give one a knowledge of the quantity of bismuth necessary to cure spontaneous spirochaetosis in rabbits. In every experiment disappearance of the spirochaetes was brought about, perhaps more slowly in Experiment No. 1, where the smallest dose was given. In every instance the doses were smaller than the toxic and fatal doses and give some idea of the power of the metal to cure. Comparing the minimum curative dose of 0.44 mgs. per kilo with the fatal dose and the maximum tolerated dose in rabbits, some interesting coefficients are got:

If/

If one takes the curative dose as 0.44 mgs. bismuth metal per kilo and the maximum dose tolerated without symptoms as 6.67 mgs. metal per kilo, there is obtained a $^{C}/_{T}$ coefficient of 1:15 for rabbits.

Taking 22.3 mgs. bismuth metal per kilo as the minimum fatal dose, there is obtained a coefficient between the lethal and maximum dose tolerated without symptoms of 3:1 for rabbits.

V. /

V. SUMMARY AND CONCLUSIONS.

The results of previous investigations into the toxicity of bismuth salts when injected intravenously have been reviewed, and it is pointed out that while stress has been laid on the symptoms of nervous system irritation, comparatively little has been written about the action on the circulatory system, though impairment of this system seems to have been noted constantly.

The minimum fatal dose and the maximum dose tolerated without symptoms have been determined in animals after intravenous injections of one of the soluble salts of bismuth.

Observations are recorded on unanaesthetised animals poisoned by the intravenous injection of the bismuth salt. The experiments show that marked cardiac impairment follows the injection of non-fatal doses, that after fatal doses death is accompanied by circulatory failure and that after multiples of the fatal dose symptoms indicative of irritation of the nervous system accompany the cardiac changes. Symptoms of gastro-intestinal and urinary tract irritation occur in the more chronic forms of poisoning, the metal being excreted in the urine from the first to the seventh or tenth day.

The action of bismuth on the circulatory system

has/

has been studied in detail. Kymographic and electrocardiographic experiments on the heart *in situ* in dogs and cats show that bismuth has a marked local toxic action on the heart muscle, the inhibitory mechanism taking no part in the production of the changes.

Doses which are a tenth of the fatal dose in cats give slight changes in the rate and amplitude of the heart beat and larger doses produce more marked impairment, characterised, *inter alia*, by slowing of the heart rate, lengthening of auriculo-ventricular conduction and pronounced irregularities in rhythm. All the fundamental functions of the heart muscle are affected: thus, stimulus production, excitability, conductivity, contractility and tonicity are lessened, the effect on conduction being the most marked and occurring after doses which have comparatively little effect on the other functions. Most of these changes also occur in perfused rabbits' hearts.

Intravenous injections of bismuth cause marked lowering of the blood pressure, a lowering which is secondary to the changes in the heart. The fall in blood pressure and the changes in the heart are influenced by the rate at which the injection is given. A second injection gives more pronounced changes, *caeteris paribus*, than the first.

The actions of some other heavy metals on the circulatory system were investigated and compared with/

with those of bismuth. Mercury and copper present marked similarity to bismuth in their effects; antimony, zinc and iron present a somewhat distant similarity; and nickel, tin, manganese and chromium, present no similarity.

Lastly, experiments were carried out on the therapeutic effect of intravenous injections of the bismuth salt in spontaneous spirochaetosis of rabbits. The results enabled me to determine the co-efficient between the curative dose and the maximum tolerated dose as 1:15, in rabbits.

I wish to thank Professor Sharpey Schafer for the use of his electrocardiograph and Dr A. D. Macdonald for the assistance he gave me by manipulating the apparatus.

I express my deep indebtedness to the late Professor A.R. Cushny, at whose instance this work was undertaken, for the facilities he afforded me and the interest he took throughout the course of the study.

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References.

(1) Orfila. Toxicologie, 1843, II, p. 10.

(2) Steinfeld and Meyer. Arch. f. exp. Path. u. Pharm. 20, p.40, 1886.

(3) Dalche and Villejean. Archiv. generale de Med. 20, p. 129, 1887.

(4) Balzer. Compt. rend. de la Soc. de Biol. 1889, p. 537.

(5) Chassevant. Annales d'Hygiene Publique, 28, p. 192, 1842.

(6) Chassevant. Dict. de Physiol. Richet. 1897, II, p. 218.

(7) Didry. Thése de Paris. 1922.

(8) Pacella. Compt. rend. de la Soc. de Biol. 88, p.388, 1923.

(9) Fritz. Orvosi Hetilap.(after Berichte) 67, p.333, 1923.

(10) Sazerac and Levaditi Compt. rend. de l'Acad. des. Sciences. 173, p.1201, 1921.

(11) Giemsa. Münch. Med. Woch. 41, p.1452, 1922.

(12) Sazerac and Levaditi. Annales de l'Institut Pasteur, 36, p. 1, 1922.

(13) Jeanselme,Chevalier, Pomaret,Blamoutier, and Joann. Bull. de la Soc. de Dermat. et Syphil. 29, p. 14, 1922.

(14) /

(14) Pomaret and Didry. Bull. de la Soc. de Dermat. et Syphil. 30, p. 197, 1923.

(15) Muller, Blass and Kratzeisen. Münch. Med. Woch. 20, p.625, 1923.

(16) Fourcade, Jalloustre and Lemay. Compt. rend. de la Soc. de Biol. 86, p.815, 1922.

(17) Grenet and Drouin. Compt. rend. de l'Acad. des Sciences, 174, p.647, 1922.

(18) Lacapere and Galliot. Bull. de la Soc. de Derm. et Syphil. 29, p. 210, 1922.

(19) Bergeret and Mayençon. Journ. de l'Anat. 9, p. 243, 1873.

(20) Fairley and Burrell. Journ. Soc. Chem. Industry. 37, p. 155, 1918.

(21) Lemay and Jalloustre. Compt. rend. de la Soc. de Biol. 88, p.474, 1923.

(22) Demelin. Thèse de Paris. 1922.

(23) Lomholt. Brit. Journ. Ven. Diseases, 1, No. I, p. 50.

(24) Rüdisule. (Barthe-) Nachweis. Bestimmung und Trennung der Chemischen Elemente, Band 3, p. 399.

(25) Kammerer. Journ. Amer. Chem. Soc. 25, p. 83, 1903.

(26) Fournier and Guenot. Bull. de la Soc. de Derm. et Syphil. 10th Nov. 1921.

(27) Bardet. Thèse de Paris. 1923.

(28) /

(28) Aubry. Journ. de Pharm. et Chem. 25, p. 15, 1922.

(29) Sazerac and Levaditi. Compt. rend. de l'Acad. des Sciences, 172, p.1391, 1921.

(30) Do. do. Compt. rend. de la Soc. de Biol. 86, p.1064, 1922.

(31) Do. do. Ibid. 86, p. 817, 1922.

(32) Robert and Sauton. Annales de l'Instit. Pasteur, 30, p. 261, 1916.

(33) Levaditi. Journ. State Med. 32, p. 62, 1924.

(34) Levaditi, Nicolau, Salgue and Schoen. Compt. rend.de l'Acad. des Sciences, 179, p.939, 1924.

(35) Levaditi. Le Bismuth dans le traitement de la Syphilis. Masson et Cie., Paris. 1924.

TABLE I.

TABLE I.

Experiment No. 1 - Cat No.4, weight 2670 grams.

Bismuth sodium tartrate 2% in doses as stated by jugular vein.

Time	Heart rate per 10 seconds	Blood pressure in mm. from base line	Vent. diast. in mm. from base line	Vent. systole in mm. from base line	Vent. Ampl. in mm.	Aur. diast. in mm. from base line	Aur. sustole in mm. from base line	Auric. Ampl. in mm.	Remarks
5 mins.	31	122	65	111	46	165	211	46	Slight slowing of heart rate. Lowering of blood pressure. Lessened ampl.of vent. and auricle
6m.10s.	1.34 mgs. bismuth metal per kilo intravenously								
7 mins		120	65	98	33	164	203	39	
7m.30s.	29	118	65	97	32	165	203	38	
8m.10s.	29	82	62	93	34	168	202	34	
8m.20s.	29	88	62	93	34	168	202	34	
9m.40s.	29	118	71	92	21	163	208	45	
10m.20s.	29	116	65	98	33	164	203	39	
13 mins	31	124	64	110	46	165	210	45	
17 mins.	31	124	65	110	45	164	210	46	Recovery of rate, blood pressure and amplitude.
17m.10s.	1.8 mgs. bismuth metal per kilo intravenously								
	A V								
17.30s.	24 24	50							Amplitudes of auricle and ventricle diminished and irregular in size. Some missed ventricular beats.
18 mins.	- -	82				196			Lessening of amplitude of auricle and ventricle. Then auricle and ventricle stop beating for 10 secs.
18m.10s.	14 14	50							Auricle and ventricle beat for 5 secs. Irregularity in amplitude.
18.15s.	24 -	Base line	78						Auricle normal rhythm but lessened amplitude; ventricle at a standstill in diastole.
18m.25s.	25 8	48	53	92	39	178	215	37	Short period of 3-1 auriculo-ventricular block.
18.30s.	25 -	Base line	73			182	208	26	Short period of complete auriculo-ventricular block.
18m.35s.	25 9	48							Ventricle responds by 3-1 block for a period of 5 secs.
18m.50s.	24 0	Base line							Complete heart block. Auricle beats with lessened amplitude but ventricle does not respond.
20mins.	Same	do.							
23 mins.	Same	do.							
27 mins.	Same	do.							
29m.30s.	24 24	48	65	106	41	170	208	38	Recovery of normal rhythm. Amplitude of auricle and ventricle small in size.
33 mins.	25 25	54	64	110	46	170	208	38	Recovery of normal rhythm and to a large extent of normal rate and amplitude.

TABLE II.

TABLE II.

Experiment No. 2 - Cat No.5, weight 2600 grams.

Bismuth sodium tartrate 1% solution by burette into jugular vein at rate of 1 c.c. per 10 mins. and the amount given marked at intervals in the record. Usual heart preparation.

Time	Bismuth metal given during expt.	Heart rate per 10 seconds	Blood pressure in mm. from base line	Vent. diast. in mm. from base line	Vent. systole in mm. from base line	Vent. ampl. in mm.	Aur. diast. in mm. from base line.	Aur. systole in mm. from base line	Aur. Apml. in mms.	Remarks.
1 min.	off	28	90	93	139	46	186	212		
2 mins.	on	27	90	93	137	44	187	212		
4 mins.	on	26	82	94	138	44	186	211		
7 mins.	on	27	78	95	141	46	186	210		
8m.30s.	on	26	76	93	139	46	187	209	22	Slight alternation of ventricular beats. Heart not slowed. Blood pressure lowered. Lessened amplitudes of anurcle and ventricle.
9m.4s.	on	26	56	Same						For 12 secs. there is a triple rhythm due to ventricular extrasystoles, superimposed on 3-1 heart block. Amplitudes of auricle and ventricle lessene
9m.20s.	on	27	56							For 36 secs. there is a double rhythm of ventricle due to idio-ventricular beats superimposed on 2-1 heart block. More marked lessening of auricular and ventricular amplitudes
9m.24s.	off									
9m.56s.	off	27	56							Double rhythm of ventricle as above.
10 mins.	off	27	56							
10m.22s.	off	28	72	94	138	44	189	208	19	Recovery of previous rate, rhythm and amplitude after the bismuth salt infusion has been stopped for 1 min.
	1.78 mgs. bismuth metal per kilo given									
13 mins.	off	28	80	94	142	48	190	212	22	
13m.5s.	on									
13m.20s.	on	28	70	96	141	45	186	210	24	
13m.50s.	on	26	58	102	150	48	188	209	21	Short period of increased systole of ventricle. Rate slowed.
13m.54s.	on	25	52	101	149	46	188	209	21	Coupled rhythm of ventricle as above. Amplitudes lessened.
15 mins.	on	25	42	Same						Coupled rhythm of ventricle.
20 mins.	on	26	60	93	141	48	191	207	16	Recovery of normal rhythm
	3.6 mgs. bismuth metal per kilo given									
23 mins.	on	26	62	95	136	41	188	210	22	
24 mins.	on	26	56	95	136	41	188	210	22	
24m.2s.	on		50	104	143	39	190	208	18	Increased systole of ventricle and slight lengthening of ventricular diastasis.
24m.6s.	on	25	42							Coupled rhythm of the ventricle due to ventricular extrasystoles.
24m.46s.	on		52	98	142	44	192	207	15	
24m.50s.	on	A V 25 13	42	103	137	34	192	208	16	2-1 Auriculo-ventricular block with marked lessening of amplitudes of auricle and ventricle and increased diastole of ventricle.
25 mins.	on	25 8	38	100	131	31	192	203	11	3-1 auriculo-ventricular block. Lessened amplitudes of auricle and ventricle. Rate of auricle slowed. Blood pressure lowered.
31 mins.	on		Same							
34 mins.	on	25 8	38	103	127	24	191	202	11	3-1 block.
38 mins.		- -	Base line							Ventricle has stopped in diastole. Auricle beats weakly for 10 secs. and then stops in diastole. Blood pressure at base line.

5.8 mgs. bismuth metal given during experiment.

TABLE III.

Experiment No. 3 - Cat No.6, weight 2250 grams. Decapitated.

Ether anaesthesia. Usual heart preparation. Bismuth sodium tartrate by injection intravenously.

Time	Heart rate per ten seconds	Blood pressure in mm. from base line	Vent. diast. in mm. from base	Vent. systole in mm. from base line	Vent. Ampl. in mm.	Aur. diast. in mm. from base line	Aur. systole in mm. from base line	Aur. ampl. in mm.	A-V interval in mm.	Duration of beat in	Remarks.
1 min.	32	28	41	106	65	138	172	34	2	6	
1m.40s.	1.78 mgs. bismuth metal per kilo. intravenously.										
2 mins.	32	28	47	87	40	135	168	33	2.5	5.5	Lessened amplitude of auricle and ventricle. Increased A-V interval
2m.30s.	30	24	38	78	40	139	138	19	varies		Increased diastole of ventricle. Lessened heart rate and lowered B.P.
3 mins.	30	16	41	85	44	142	159	17	3	6	There is a lengthening of auriculo-ventricular conduction and of the duration of the ventricular beats and a missed ventricular beat occurs about 1 in 20. There is a slight irregularity in rhythm in the auricle and this reflects itself occasionally in the ventricle in a beat of smaller amplitude. Blood pressure is lowered.
	A V										
3m30s.	30 26	16	varies			143	152	9			The ventricle beats in a quadruple rhythm. All are responses to auricular beats, there being no missed beats. The first two beats of the series of four are of long duration, the second two occur after the same A-V interval and are of much shorter duration and their amplitude is smaller. This irregularity terminates in 2-1 auriculo-ventricular block.
3m.50s.	29 15	22	35	75	40	145	160	15	3		
										6	
5m.20s.	27 13	22	33	76	43	145	160	15		7	
8m.10s.	25 8	22	33	78	45	143	158	15			3-1 block. Lessened amplitude of auricle and ventricle and increased diastole of ventricle.
8m.20s.	25 12	22	32	79	47	143	158	15			
11 mins.		Same									
11m.30s.	24 16	22	37	117		132	158	26			There is 3-2 auriculo-ventricular block with increased duration ofbeat and increased time of A-V conduction. This terminates in normal rhythm with a smaller diastole of the ventricle.
11m.50s.	24	22	37	117	80	136	157	21			
12m.10s.	25	22	35	115	80	136	157	21			
17 mins.	25	20	40	97	57	130	145	15			Heart has recovered its rhythm and amplitude to a large extent. Heart rate is still slow and the blood pressure is low.
18 mins.	1.78 mgs. bismuth metal per kilo intravenously.										
	A V										
18m.20s.	23 12	16	43	83	40	135	148	8			Lessened amplitude of auricle and ventricle. Every third or fourth ventricular beat is missed. Blood pressure lower. Rate slower.
18m.30s.	22 11	14	50	77	27	135	143	8			Auricular and ventricular amplitudes very much lessened and ventricular diastole increased. 2-1 block is present.
18m.40s.	21 9	12	52	75	23	132	138	6			
20mins.	18 4	12	52	75	23						Heart block of varying types 2-1, 5-2, 4-1, and 5-1. Auricular and ventricular amplitudes become very much lessened. Blood pressure very low. Heart rate slowed markedly.
22 mins.	12 3	8	50	75	25						
25 mins.	8 2	base line	47	72	25						Auricle and ventricle stop simultaneously in diastole. Blood pressure falls to base line.
27 mins.		do.		53			135				

TABLE IV.

Experiment No. 4 - Cat No. 7, weight 2250 grams. Decapitated.
Usual heart preparation. Bismuth sodium tartrate intravenously by injection.

Time	Heart rate per 10 secs.	Blood pressure in mm. from base line	Vent. diast. in mm. from base line	Vent. systole in mm. from base line	Vent. ampl. in mm.	Aur. diast. in mm. from base line	Aur. systole in mm. from base line	Aur. Ampl. in mm.	Remarks.
min.	31	22	42	135	93	140	168	28	
m.20s.	1.78 mgs. bismuth metal per kilo intravenously.								
m.30s.	27	20	50	121	71	147	166	19	Auricular and ventricular beats smaller in amplitude. Slowing of heart rate and lowering of blood pressure.
1m.40s.	A 26 V 13	18	50	103	53	149	163	14	Duration of the beat and the length of auriculo-ventricular condution are increased, and 2-1 heart block comes on. Lessened amplitudes of auricle and ventricle.
2m.20s.	27 13	20	47	113	76	151	163	12	
4m.20s.	26 8	20	50	111	61	151	163	12	Period where there is alternating 2-1 and 3-1 heart block. Blood pressure is low and rate of heart is slowed.
9 mins.	24 8	18	47	116	69	150	163	13	3-1 block. A-V condution and duration of beat increased.
10m.10s.	24 12	20	46	122	76	149	162	13	
14 mins.	25	20	45	131	86	144	162	18	Heart has recovered a regular rhythm.
17 mins	25	20	51	120	69	135	162	27	
22 mins.	26	20	51	121	70	140	162	22	Heart has recovered to a large extent its former rhythm and amplitude. Heart rate is still slowed and blood pressure is still low.
22.30s.	1.78 mgs. bismuth metal per kilo intravenously								
22.40s.	A 24 V 8	16	56	100	44	146	156	10	Lessening of amplitude of ventricular beats. Lengthening of A-V conduction and duration of beat. Heart block of a regular 3-1 type ensues.
23m.10s.	22 11	16	53	97	44	143	156	10	2-1 heart block. Increase in diastole of auricle and ventricle.
24m.30s.	24 12	18	53	107	54	143	153	10	
26m.20s.	24 8	16	48	106	58	143	152	9	
27 mins.	Same								
30 mins.									Alternating 2-1 and 3-1 heart block. Systole of the ventricle in2-1 heart block is higher than in 3-1 block.
33 mins.	Same							9	
35 mins.	24 12	16	50	118	68	143	152	10	2-1 heart block. Amplitudes of auricle and ventricle much diminished. The blood pressure is low.
40 mins.	24 12	16	56	108	52	142	152		
44 mins.	24 24	18	40	97	57	140	153	13	
48 mins.	24 24	18	40	100	60	140	153	13	Heart has recovered a normal rhythm and amplitude of auricle and ventricle have recovered to a certain extent. Heart rate is still slow and blood pressure is low.

TABLE V.

Experiment No.5, Cat No. 8, weight 2600 grams. Both vagi cut in neck.

Bismuth sodium tartrate 1% given by burette into jugular vein at rate of 1 c.c. per 10 mins, and the amount given marked at intervals in the record.

Time	Bismuth metal given	Heart rate per 10 seconds	Blood pressure in mm. from base line	Vent. diast. in mm. from base line	Vent. systole in mm. from base line	Vent. ampl. in mm.	Aur. diast. in mm. from base line	Aur. systole in mm. from base line	Aur. Ampl. in mm.	Remarks
		33	140	97	152	55	174	216	42	Blood pressure lessened
4 mins.	on									
4m.10s.	on	32	140	99	147	48	176	216	40	Heart rate slowed.
6m.20s.	on	30	134	102	147¾	45	180	217	37	Lessened amplitudes
8m.30s.	on	29	122	102	148	46	180	217	37	of auricle and ventricle
11 mins.	on	29	122	102	148	46	180	217	37	
16 mins.	on	28	122	101	145	44	180	213	33	
17m.30s.	on	27	108	99	151	52	183	210	27	
18 mins.	on	27	100	98	152	54	185	208	23	
20 mins.	on	27	100	100	148	48	184	210	26	
	1.78 mgs. bismuth metal per kilo. infused.									
	Stop infusion for 20 seconds.									
22m.30s.	on	38	106	98	144	46	183	214	31	Blood pressure and heart rate have recovered partly. Amplitudes of auricle and ventricle have recovered partly.
24 mins.	on	27	102	98	148	50	185	211	26	
27 mins.	on	28	94	96	147	51	186	212	26	
28m.10s.	on	27	74							Slight alternation of ventricular beats. B.P. lowered and rate slowed.
29m.20s.	on	26	80	94	148	54	187	207	20	
32 mins.	on	27	88	93	142	49	187	210	23	There is a movement of the ventricular lever towards systole for a few beats before the onset ofextrasystoles.
33m.30s.	on	26	74	91	144	53	190	208	18	
33m.50s.	on	26	56							Coupled rhythm of ventricle for a period of about 8 secs. Every normal beat is followed by a ventricular extrasystole and later by two ventricular extrasystoles making a triple rhythm,
34m.10s.to 30s.	on	A V 29 14	64	106	149	43	188	207	19 →	There is 2-1 heart block, and lessened amplitudes of the auricle and ventricle. Auricular rate is slowed. Blood pressure is low.
	Bismuth influsion stopped for 30 seconds									
34m.54s.		30	84	94	146	52	191	206	15	Heart has recovered a normal rhythm and part of its former rate. Amplitudes of auricle and ventricle recover slightly. Blood pressure recovers to some extent.
38 mins.		29	90	95	138	43	186	213	27	

TABLE V.

TABLE VI.

TABLE VI.

Experiment No. 6 - Cat No. 9, weight 2605 grams.

Bismuth sodium tartrate in 2% solution run into jugular vein through 2 c.c. burette, and the amount given marked at intervals in the record. Usual heart preparation.

Time	Bismuth metal given	Heart rate rate per 10 secs.	Blood pressure in mm. from base line	Vent. diast. in mm. from base line	Vent. systole in mm. from base line	Vent. ampl. in mm.	Aur. diast in mm. from base line	Aur. systole in mm. from base line	Aur. Ampl. in mms.	Remarks.
0 mins.	off	31	90	101	154	53	168	225	57	
30 secs.	on	29	88	104	158	54	168	225	57	Increased amplitude and increased systole of the ventricle. Lessened amplitude of auricle. Then there is a short period of alternation in the ventricular beats.
1 min.	on	29	86	106	163	57	172	222	50	
1m.20s.	on	29	78				171	218	47	
1m.30s.	on	29	76	108	162	54	178	216	38	
2m.10s.	on	29	84	109	165	56	175	218	43	
4 mins.	on	29	82	108	157	49	169	221	53	Rate of heart slowed. B.P. lowered. Ventricular and auricular amplitudes lessened.
5m.10s.	on	27	68	109	153	44	171	216	45	
6m.30s.	on	27	72	109	153	44	170	215	45	
6m.40s.	on	27	48	109	153	44	177	200	23	There is marked lessening of the amplitude of the auricle and to a less extent of the ventricle. Then 2-1 heart block ensues without previous irregularity. It is accompanied by an alternation in the amplitude of the auricular beats due to the blocking of the blood flow from auricle to ventricle.
6.46s.	on	26	34	111	152	41	178	191		
6m.50s.	on	A V 25 13	44	111	147	36				
7m.2s.	on	25 5	28	108	138	30				Heart block increases from 4-1 to 5-1 and then 6-1 in a few seconds. Auricular and ventricular amplitudes much smaller. B.P. low.
	3.6 mgs. bismuth metal per kilo given									
9 mins.	on	24 6	40	107	135	28	188	206	18	
10 mins.	on	Same								
13 mins.	on	24 6	46	107	134	27	192	212	20	
15 mins.	on	24 8	58	103	136	33	181	212	31	A regular 3-1 block. The ventricle shows a rhythmic type of alternation. Amplitudes of auricle and ventricle small.
19 mins.	on	Same								
21 mins.	7.2 mgs. bismuth metal per kilo given.									
25 mins.	on	24 5	38	113	138	25	194	207	13	5-1 block. Lengths of auriculo-ventricular conduction and duration of the beats increased.
28 mins.	on	22 5	40	104	132	28	193	203	10	4-1 block. Marked lessening of amplitudes of auricle and ventricle. Systole of ventricle is decreased much more than diastole of ventricle. Blood pressure much lowered.
29 mins.	on	22 4								5-1 block.
32 mins.	10.8 mgs. bismuth metal per kilo given.									
	on	23 4	38	118	136	18				
35 mins.	on	20 5	30	119	138	19				
37 mins.	on	Same								
40 mins.	on	20 5	40	121	143	22				4-1 block. Amplitude of the auricle and ventricle have undergone very marked diminution; their diastoles are increased slightly. Blood pressure very low. Auricular rate slowed markedly.
45 mins.	14.4 mgs. bismuth metal per kilo given									
50 mins.	on	Same								Heart continued in the same state for 10 mins. until 18 mgs. bismuth metal per kilo had been given.

Table VII.

TABLE VII.

Experiment No. 7, Dog No. 1, weight 6.5 kilo. Cushny myocardiograph used. Usual heart preparation. Right vagus nerve prepared for stimulation. Bismuth 2% solution given by 2 c.c. burette at rate of 1 c.c. per 10 mins. and the amount given marked at intervals in the record.

Time	Bismuth metal given	Heart rate per 10	Blood pressure in mm. from base line	Vent. diast. in mm. from base line	Vent. systole in mm. from base line	Vent. ampl. in mm	Aur. diast. in mm. from base line	Aur. systole in mm. from base line	Aur. ampl. in mm.	A-V interval in mm.	Duration of beat in mm.	Remarks
1 min.	Minimum stimulation of vagus given. Slowing of heart from 16-14									1.3	8	
5 mins.	off	18	102	104	160	56	188	198	10	1.3	3	
5m.2s.	on											
6m.40s.	on	18	102	105	156	51	190	196	6	1.75	8	
7m.40s.	on	18	98	111	164	53	190	201	11	-	-	Increased systole of the ventricular beats. Lessening of amplitude of the auricular beats.
8 mins.	on	A V 18 -	84	112	173	61	190	201	11	2.8	9	The duration of A-V conduction is increased and the duration of the ventricular beat is increased to such an extent that every second or third beat falls on an incompletely relaxed ventricle and is abortive, merely notching the down-stroke of the ventricular lever.
8m.8s.	on	17 11	78	114	176	62	190	199	9	3.5	10	The abortive beats become rarer and 2-1 heart block sets in.
8m.14s.	off	1.8 mgs. bismuth metal per kilo given.										Abortive beats occur as before. Amplitudes of auricle and ventricle lessened. Fall in blood pressure.
12 mins.	on	18	102	109	159	50	188	225	37	2.0	8	Heart has recovered to a large extent in amplitude and rhythm. Blood pressure has recovered.
12m.40s.	on											
12m.50s.	on		100	109	158	49	189	202	13	-		
12m.58s.	on	17	102	112	161	49	190	200	10	2	8	Lengthening of period of ventricular diastasis.
14 mins.	on	18	96	115	170	55	190	202	12	2.8	8	Systole of the ventricle is increased and the beats are in sets of 3 and 2.
	2.7 mgs. bismuth metal per kilo given.											
15 mins.	on	20 A V	68	112	155	43	189	216	27	3		
15m.8s.	on Stim. of vagus given	20 10	82	113	172	59	189	216	27	3.1	11	The ventricular beats are of small amplitude and of varying duration. 2-1 heart block comes on. Stimulation of the vagus with the same strength of current as used before gives slowing and stopping of both auricle and ventricle.
17 mins.	on	21 16	78	108	171	63	186	219	33	3	8	Onset of 2-1 block of incomplete type in which occasional abortive beats of the ventricle occur.
18 mins.	on	21 17	78	100	171	63	186	219	33	3	8	Abortive beats which are responses to auricular stimuli occur every third beat. Duration of ventricular beats increased and A-V conduction lengthened.
20m.30s.	on	21 11	76	111	165	54	185	222	37	4	8	
22 mins.	on	21 10	78	108	150	42	189	224	35	4	10	Systole of the ventricle lessened but diastole increased.
23m.10s.	on	22 18	-	118	147	29	188	213	25			
24m.6s.	on	22 16	36	118	145	27	190	209	19			There comes on suddenly complete auriculo-ventricular heart block with a spontaneous rhythm of the ventricle. Then the heart rate becomes slower, the amplitude of auricle and ventricle less and the ventricular responses an irregular mixture of spontaneous rhythm and responses to auricular beats.
	4.2 mgs. bismuth metal per kilo given.											
25 mins.				130			201					Auricle stops in diastole. Ventricle undergoes a coarse fibrillation in mid-diastole and stops a few seconds later in diastole.

TABLE VIII.

TABLE VIII

Experiment No. 8 - Dog No. 2, weight 7.5 kilo. Cushny myocardiograph used. Bismuth sodium tartrate 2% solution into jugular vein through 2 c.c. burette and the amount given marked at intervals in the record.

Time	Bismuth metal given	Heart rate per 10 seconds	Blood pressure in mm. from base line	Vent. diast. in mm. from base line	Vent. systole in mm. from base line	Vent. ampl. in mm.	Aur. diast. in mm. from base line	Aur. systole in mm. from base line	Aur. ampl. in mm.	A-V inter- in mm.	Duration of vent. beat in mm.	Remarks
5 mins.	off	22	96	102	129	27	166	203	37	2	5	
6 mins.	on											
7m.40s.	on	24	96	102	130	28	166	203	37	2	5	Slight quickening of heart rate
8m.8s.	on	25	96	104	121	17	166	201	35	2	5	Lessening of systole of ventricle.
8m.52s.	on	A V 26 19	74	102	122	20	168	207	39	2.5	6	The length of A-V conduction is increased. Duration of ventricular beats increased. One ventricular beat is missed every 3rd beat and the next ventricular beat is followed by a small and abortive beat occurring before relaxation of the ventricle is complete.
9m.28s.	on	27 14	68	101	119	18	168	215	47	3	6	There is 2-1 block of irregular type in that after every 8th beat an abortive ventricular beat occurs. Quickening of heart rate. Lengthened A-V conduction and increase of auricular amplitude. Direct observation of the heart shows that the ventricular contraction passes more slowly over the heart muscle.
10 mins.		1.78 mgs. bismuth metal per kilo given										
10m.11s.	off											
12m.4s.	on	27	88	101	120	19	171	210	39	2.1		
12m.30s.	on	27	88	100	119	19	171	218	47	2.1		
12m.36s.	on	A V 28 26	78				170	225	55	3		There is a period of irregular 3-2 A-V block combined with abortive ventricular beats and this series alternates with a normal rhythm. A few ventricular extrasystoles occur. Ventricular amplitude lessened and blood pressure lowered.
12m.50s.	on	28 23	78	102	126	24	171	230	59	3		
13m.20s.	on	28 22	76	102	120	18	171	227	56	3		
14 mins.	on	29 14	76	99	121	22	172	232	60	3	6	2-1 block comes on. There is an alternation in the beats of the auricle.
15 mins.	on	29 14	72	99	121	22	172	229	57	3	6	
17 mins.	on	28 14	58	99	115	16	178	201	23	4	7	2-1 block. Amplitudes of auricle and ventricle become small, the rate does not alter, the A-V interval and duration of ventricular beats becomes lengthened, the strength of the ventricular beats becomes irregular and finally both chambers stop in diastole.
19 mins.		4.45 mgs. bismuth metal per kilo given.										
26 mins.	on											Bismuth infusion stopped and the auricle and ventricle recover in 5 mins. to their state at 17 mins.
31 mins.	off	26 20	50	106	115	9	180	196	16			
35 mins.	off	Same										

TABLE IX.

TABLE IX.

Experiment No. 10 - Cat No. 11, weight 2470 grams.

Usual heart preparation.

Time	Heart rate per 10	Blood pressure in mm. from base line	Vent. diast. in mm. from base line	Vent. systole in mm. from base line	Vent ampl. in mm.	Aur. diast. in mm. from base line	Aur. systole in mm. from base line	Aur. ampl. in mm.	A-V interval in mm.	Duration of vent. beat in mm.	Remarks
12 mins.	33	110	85	131	46	167	219	52	2	5	
13m.2s.	0.45 mgs. bismuth metal per kilo intravenously										
13m.20s.	32	110	88	126	38	168	217	49	2	5	
13m.36s.	30	104	90	131	41	170	215	45	2	5	Lessening of auricular amplitude. Lessening of ventricular amplitude. Slowing of heart rate and fall in blood pressure.
14 mins.	31	104	86	135	49	174	209	35	2	5	
15m.2s.	31	108	84	134	50	170	202	32	2	5	
15m.32s.	31	110	86	130	44	171	216	45	2	5	
23 mins.	32	110	83	129	47	167	217	50	2	5	
30 mins.	31	108	79	134	55	167	220	53	2	5	
30m.20s.	2.67 mgs. bismuth metal per kilo intravenously										
30m.30s.	30	106	80	126	46	167	215	48	2	5	
30m.52s.	30	90	82	137	55	180	195	15	2	5.5	
31 mins.	30	84	?	?	?	182	192	10	-	-	The ventricle beats in a quadruple rhythm. Of the series the first beat occurs after a long diastole and is small inamplitude and of long duration. The next occurs after a shorter A-V interval and has larger systolic amplitude. The next two occur before the ventricle is relaxed and are apparently ventricular extrasystoles. Then there is a long diastasis until the next series begins. This irregularity becomes a triple rhythm and than a double rhythm and then a simple 2-1 block. This irregular state lasts 10 seconds.
	A V										
31m.16s.	28 14	102	91	130	39	192	206	14	3	6	2-1 block. Blood pressure lowered. Heart rate slowed. Ventricular and auricular amplitudes smaller.
31m.50s.	28 14	94	89	131	42	189	202	13	4	6	2-1 block.
32m.22s.	28 14	104	95	117	22	193	203	10	3	6	The size of the ventricular beats have changed. The A-V interval is shorter and the duration of beats is the same, but the systole is very much smaller. This irregularity passes off in 30 seconds.
32m.58s.	27 14	104	94	132	38	193	203	10	2.5	5.5	
36 mins.	27 14	108	89	117	29	190	213	23	2.5	6	
36m.40s.	28	106	Varies								The ventricle shows coupled rhythm, there being no response to every 3rd auricular beat. Every second beat in the coupled ventricular rhythm is larger in size, probably the result of a preceding shorter diastasis with a consequently smaller amount of blood for the ventricle to propel
37 mins.	28 21	106	Irregular								The ventricle beats in sets of 5. The first beat of the series is of long duration; the next shorter; the next occurs before diastole is complete; then there is a missed beat; then a large beat; then another missed beat, and the series is repeated.
40 mins.	29	106	Irregular								
43 mins.	29 24	104	Varies								The ventricle beats in sets of 5. First beat normal; next normal; next occurs before diastole is completed and is abortive; the next two are extrasystoles followed by a missed beat.
44m.4s.	29 -	102									Ventricle beats in sets of 6. First 3 normal; next occurs before diastole is complete; next two are extrasystoles followed by amissed beat. A-V conduction varies in these beats, being longer in the first beats of the series.
44m.42s.	29 28	112	91	141	50	190	212	22	3		
50 mins.		Same									

TABLE X.

TABLE X.

Experiment No. 11, Dog No. 3, weight 5700 grams. Cushny myocardiograph used. Right vagus nerve prepared in the neck. Bismuth sodium tartrate intravenously by injection, and amount given marked at intervals in the record.

Time	Heart rate per 10 seconds	Blood pressure in mm. from base line	Vent. diast. in mm. from base line	Vent. systole in mm. from base line	Vent. ampl. in mm.	Aur. diast. in mm. from base line	Aur. systole in mm. from base line	Aur. ampl. in mm.	A-V interval in mm.	Duration of vent. beat in mm.	Remarks.
10 mins.											Stim. vagus (coils separated 13 cm.) gives stopping of heart.
11 mins.											Stim. vagus (coils separated 14 cm.) gives no change in heart
15 mins.	33	84	70	137	63	167	203	36	3	5	
16m.10s.	0.54 mgs. bismuth metal per kilo intravenously										
16m.34s.	31	78	70	135	66	171	198	27			
16m.50s.	32	82	70	135	65	173	198	26			Lessening of amplitude of auricle. Increase in diastole and amplitude of ventricle. Slight slowing of heart rate.
17m.30s.	30	84	66	135	69	172	197	25			
19m.44s.	32	86	66	132	66	169	200	30			
21m.20s.	32	84	66	132	66	169	200	31			Heart rate and amplitude partly recovered.
22 mins.	0.05 mgs. atropine per kilo intravenously										
23 mins.	32	84	66	132	66	169	200	31			
24 mins.											Stim. vagus (coils separated 12 cm.) gives slight slowing.
26 mins.	0.05 mgs. atropine per kilo intravenously										
28 mins.	32										Stim. vagus (coils separated 13 cm.) gives no slowing.
38 mins,	32	86	66	139	73	166	204	38			
39 mins.	0.54 mgs. bismuth metal per kilo intravenously										
39m.10s.	32	80	66	137	71	168	200	32	3		
39m.50s.	30	82	65	139	74	170	200	30			
41 mins.	29	86	64	141	77	170	200	30			
46 mins.	29	84	66	140	74	167	204	37			Changes in amplitude and rate similar to those noted after the first dose.
51 mins.	29	66	66	141	73	165	202	37			
53 mins.	29	66	66	141	73	165	202	37			Slight increase in A-V interval and in the duration of the ventricular beats.
54m.10s. to 54m.20s.	2.67 mgs. bismuth metal per kilo. intravenously.										
54m.26s.	25	64	65	140	75	170	197	27	3.1	5.2	
54m.50s.	25	64	61	135	74	173	192	19			
55m.14s.	24	62	60	135	75	173	191	18	3.5	5.5	
56 mins.	23	62	60	129	69	176	192	16	3.5	6	Fall in blood pressure and slowing of heart rate. Lessening of auricular and ventricular amplitudes with increase in ventricular diastole.
56m.16s.	-	30	62	121	59	175	194	19			Irregularity of the ventricle has started. There is a lengthened A-V conduction and increased duration of the ventricular beats. The ventricle beats in a coupled rhythm, one prolonged beat being followed by an abortive beat which merely notches the downstroke of the ventricular lever. There are ventricular extrasystoles every 3rd or 4th beat. The auricle shows an irregularity of the alternans type due to the disturbance in the passage of blood from the auricle to the ventricle.
56m.24s.	-	-	62	123	61	178	191	13		7	Extrasystoles have stopped. The abortive beats become smaller and smaller and stop and 2-1 block ensues. There is slowing and lessened amplitude of auricle and ventricle with increased diastole of the ventricle.
57m.10s.	-	-	59	110	51	180	192	12			
61m.30s.	-	-	58	102	44	184	205	21			3-1 block with lessened ventricular amplitude and increased diastole of ventricle.
67 mins.	-	-	49	115	66	183	205	22			

TABLE X (Contd.).

Experiment No. 11(Contd.)

TABLE X (Contd.).

Time	Heart rate per 10 secs.	Blood pressure in mm. from base	Vent. diast. in mm. from base	Vent. systole in mm. from base	Vent. ampl. in mm.	Aur. diast. in mm. from base	Aur. systole in mm. from base	Aur. ampl. in mm.	Aur. interval in mm.	Duration of vent. beat in mm.	Remarks.
69 mins.	-	-	49	113	64	183	205	22			Apparent 4-1 block, each ventricular beat being followed by an abortive contraction which seems to follow an auricular beat. A few seconds later there occurs after every 7th ventricular beat a ventricular beat which is not accompanied by an abortive beat because it occurs earlier than its precursors by one auricular impulse.
73 mins.	-	-	49	142	93	176	198	22			The increase of the diastole of the ventricle is more marked. Amplitudes of auricle and ventricle have improved. The ventricle only missed one beat here and there.
86 mins.	-	-	55	145	90	168	200	32			Auricle and ventricle regular. The amplitudes have recovered to a great extent.

Experiment ended.